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4 mL of dry acetonitrile were added, and the mixture was stirred overnight. After filtration to remove a small amount of insoluble solid, the mixture was concentrated to dryness under reduced pressure. The residual oil was redissolved in 4 mL of acetonitrile, and with ice cooling, 0.16 mL of methanol was added. The mixture was stirred for 1 min and allowed to stand for 3 min, before filtering. After the mixture was washed with three 3-mL portions of acetonitrile and dried under reduced pressure, 530 mg of product was obtained: NMR (Me_2SO-d_6) δ 1.36 (s, 12 H, *t*-Bu and CH_3), 1.40 (s, 3 H, CH_3), 3.12 (s, 3 H, NCH_3), 3.40-3.86 (m, 9 H, 4 × NCH_2 and CH of SCH_2), 3.96 (d, 1 H, J_{gem} = 16 Hz, CH of SCH_2), 4.40, 4.66 (AB, 2 H, J_{gem} = 13 Hz, NCH_2), 4.62-5.06 (m, 4 H, NCH_2CH_2F), 5.26 (d, 1 H, J = 5 Hz, CH), 5.93 (dd, 1 H, J = 5 and 7 Hz, CH), 6.68 (s, 1 H, Ar), 7.25 (s, 2 H, NH_2), 7.92 (d, 1 H, J = 12 Hz, Ar), 8.88 (s, 1 H, =CH-), 9.44 (d, 1 H, J = 7 Hz, NH).

Acknowledgment. We thank members of our Physical Chemistry Department for providing spectral data, especially Mr. Gino Sasso who assisted in interpretation of NMR spectra. We gratefully acknowledge the assistance of Ms. BettyAnn Hedemus in preparing the manuscript.

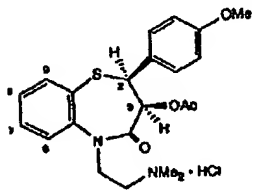
Synthesis of Halogen-Substituted 1,5-Benzothiazepine Derivatives and Their Vasodilating and Hypotensive Activities

Hirozumi Inoue,*,† Mikihiko Konda,† Tomiki Hashiyama,† Hisao Otsuka,† Kaoru Takahashi, Mitsunori Gaino,† Tadamasa Date,† Keiichi Aoe,† Mikio Takeda,† Sakae Murata,‡ Hiroshi Narita,‡ and Taku Nagao‡,§

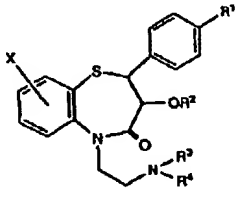
Organic Chemistry Research Laboratory and Biological Research Laboratory, Tanabe Seiyaku Co. Ltd., 2-2-50, Kawagishi, Toda, Saitama 335, Japan. *Received May 15, 1990*

In an attempt to improve the effectiveness and duration of the action of diltiazem (1), a 1,5-benzothiazepine calcium channel blocker, its derivatives (2) with halogen substituents on the fused benzene ring were synthesized. These compounds were evaluated for their effects on vertebral and coronary blood flows and antihypertensive activity. The structure-activity relationships are discussed. The 8-chloro derivative ((+)-2b), the most potent compound in this series, was selected for clinical evaluation as a cerebral vasodilating and antihypertensive agent.

Diltiazem (1)[1] is a potent calcium channel blocker and has been widely used as an effective antianginal and antihypertensive agent.[2] Our previous study[3] on the structure-activity relationships (SAR) of some 40 derivatives of 1 made clear the effect of substituents at the positions 2, 3, and 5 and their stereochemical requirements for activity. The effect of substitution on the fused benzene ring of 1, however, remained uncertain, since only the 7-chloro derivative (2, X = 7-Cl, R^1 = OMe, R^2 = Ac, R^3 = R^4 = Me) has been synthesized.[1a] In an attempt to



Diltiazem (2S, 3S) (1)



(2)

improve the effectiveness and duration of the action of diltiazem (1) and to gain further insight into the SAR, we introduced halogen substituents at the positions 6-9 of 1 in the present study. Described herein are the synthesis as well as the vasodilating and antihypertensive activities of this new series of derivatives (2). The SAR are also discussed.

Chemistry

The synthesis of *cis*-2-aryl-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4(5*H*)-one (5), a requisite intermediate for 2, is shown in Scheme I. Fusion of the halogen-substituted 2-aminothiophenol 3 with the *trans*-3-arylglycidic ester 4 at about 160 °C gave the cis lactam 5. This reaction involves cis opening of the oxiran ring of 4 by the thiol group of 3 followed by intramolecular cyclization to give the cis lactam 5 predominantly. Although the yield was rather poor, this simplest method was mainly employed for the preliminary synthesis of 5 (Table I, method A). The unwanted trans isomer 6 was isolated as a minor product in some cases (Table I, 6a,b,h,j).

The stereochemistry of these lactams (5 and 6) was deduced from the vicinal coupling constant between the methine protons at C_2 and C_3 (about 6 Hz and 11 Hz for cis and trans isomers, respectively)[4] (Table II). The reaction of 2-amino-3-chlorothiophenol (3a), bearing a substituent ortho to the amino group, with the glycidic ester 4a gave the intermediate amino ester 7e predominantly together with the lactams (5a and 6a, Table I). More practically, the cis lactam 5 was prepared via the amino ester (7) (Scheme I). Heating of 2-amino-5-chlorothiophenol (3c) with the glycidic esters 4a and 4b in a nonpolar solvent at lower temperature (65-130 °C) gave the threo amino esters 7a and 7b in moderate yield (Table III, method F). Alkaline hydrolysis of 7 gave the amino acid 10 (Table IV, method I).

Alternatively, the amino acids 10 and 11 were also obtained via the nitro esters 8 and 9. Recently, we reported that some Lewis acids, such as halides or carboxylates of tin or zinc, catalytically effect ready and highly stereose-

†Organic Chemistry Research Laboratory.
‡Biological Research Laboratory.
§Present address: Department of Toxicology and Pharmacology, Faculty of Pharmaceutical Sciences, the University of Tokyo.

(1) (a) Kugita, H.; Inoue, H.; Ikezaki, M.; Konda, M.; Takeo, S. *Chem. Pharm. Bull.* 1971, *19*, 596. (b) Inoue, H.; Takeo, S.; Kawazu, M.; Kugita, H. *Yakugaku Zasshi* 1973, *93*, 729. (c) Abe, K.; Inoue, H.; Nagao, T. *Yakugaku Zasshi* 1988, *108*, 716.
(2) (a) Yasue, H.; Omote, S.; Takizawa, A.; Nagao, M. *Circulation Research* 1983, *52*. (Suppl. I), 147. (b) Kimura, E.; Kishida, H. *Circulation* 1981, *63*, 844.
(3) (a) Nagao, T.; Sato, M.; Nakajima, H.; Kiyomoto, A. *Chem. Pharm. Bull.* 1973, *21*, 92. (b) Nagao, T.; Sato, M.; Nakajima, H.; Kiyomoto, A. *Jpn. J. Pharmacol.* 1972, *22*, 1.
(4) Kugita, H.; Inoue, H.; Ikezaki, M.; Konda, M.; Takeo, S. *Chem. Pharm. Bull.* 1970, *18*, 2284.

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Scheme I

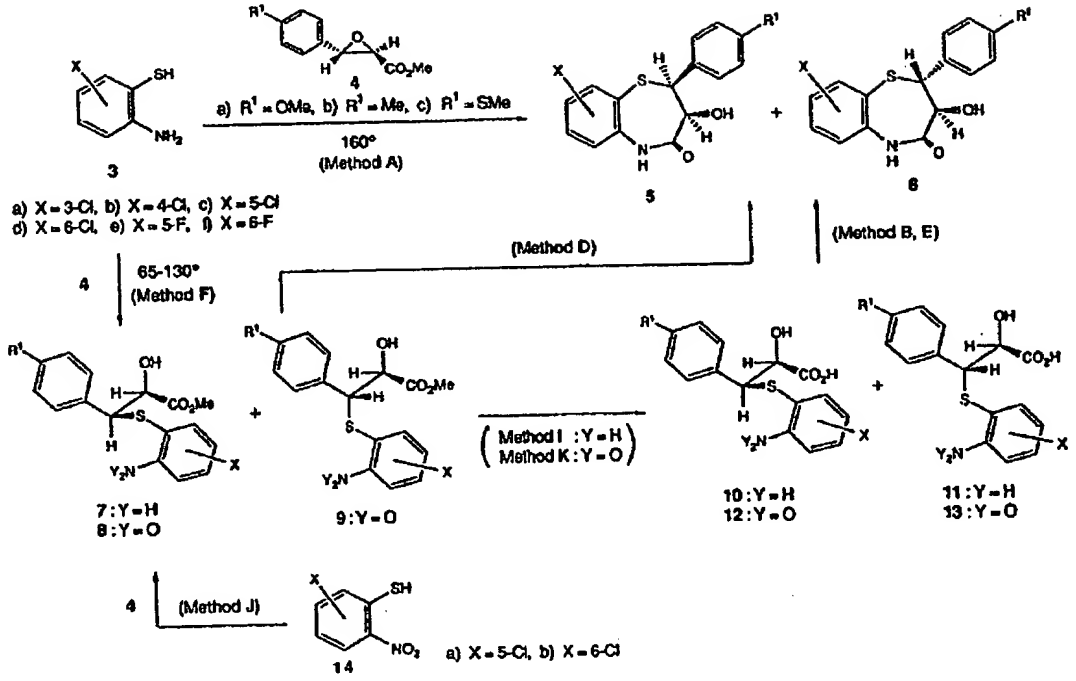
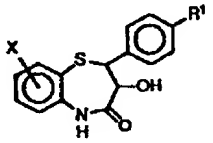


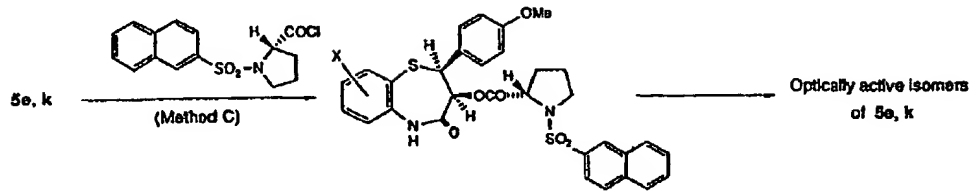
Table I. 7-Membered Lactams 5 and 6



compd	X	R¹	stereochemistry	mp, °C	synthetic method	yield,[a] %	recryst solvent[b]	formula
5a	6-Cl	OMe	cis	226.5–230.5	D	48.0	A	$C_{16}H_{14}ClNO_3S$
					A	18.7[c]		
6a	6-Cl	OMe	trans	210–211	A	3.0	A	$C_{16}H_{14}ClNO_3S$
5b	8-Cl	OMe	cis	230–232	B	80.3	B	$C_{16}H_{14}ClNO_3S$
					A	28.3[d]		
6b	8-Cl	OMe	trans	183–185	B	78.7	B	$C_{16}H_{14}ClNO_3S$
					A	3.9		
(+)-5b	8-Cl	OMe	cis	239–241[e]	B	85.7	C	$C_{16}H_{14}ClNO_3S$
(−)-5b	8-Cl	OMe	cis	238–240[f]	B	85.0	C	$C_{16}H_{14}ClNO_3S$
5c	8-Cl	SMe	cis	215–217	A	21.0	D	$C_{16}H_{14}ClNO_2S_2$
5d	8-Cl	Me	cis	195–196.5	B	84.0	B	$C_{16}H_{14}ClNO_3S$
5e	9-Cl	OMe	cis	249–252	B	70.0	E	$C_{16}H_{14}ClNO_3S$
					D	48.5		
2*S*,3*S*-5e	9-Cl	OMe	cis	187–189[g]	C	36.6	F	$C_{16}H_{14}ClNO_3S$
2*R*,3*R*-5e	9-Cl	OMe	cis	188–189[g]	C	35.8	F	$C_{16}H_{14}ClNO_3S$
					E	72.6		
5f	8-F	OMe	cis	215–218	A	15.4	G	$C_{16}H_{14}FNO_3S$
5g	8-F	Me	cis	210–213	A	7.3	G	$C_{16}H_{14}FNO_2S$
5h	9-F	OMe	cis	218–222	D	87.7	D	$C_{16}H_{14}FNO_3S$
					A	4.5[i]		
6h	9-F	OMe	trans	226–228	A	2.4	D	$C_{16}H_{14}FNO_3S$
5i	7,8-Cl_2	OMe	cis	239–243	A	19.4	A	$C_{16}H_{13}Cl_2NO_3S$
5j	8,9-Cl_2	OMe	cis	207–209	A	13.7	A	$C_{16}H_{13}Cl_2NO_3S$
6j	8,9-Cl_2	OMe	trans	244–249	A	2.7	A	$C_{16}H_{13}Cl_2NO_3S$
(+)-5k	7-Cl	OMe	cis	225–227[h]	C	27.0	B	$C_{16}H_{14}ClNO_3S$
(−)-5k	7-Cl	OMe	cis	229–232[f]	C	28.7	B	$C_{16}H_{14}ClNO_3S$

[a] No attempts were made to maximize yields. [b] A = $CHCl_3$–EtOH; B = AcOEt–*n*-hexane; C = acetone; D = DMF–EtOH; E = DMF–*i*-Pr_2O; F = aqueous MeOH; G = EtOH. [c] The trans lactam 6a and the amino ester 7e were obtained in 3.0 and 16.5% yields, respectively. [d] The trans lactam 6b was obtained in 3.9% yield. [e] $[\alpha]^{20}_D$ +92.1° (c = 1.02, DMF). [f] $[\alpha]^{20}_D$ −92.0° (c = 1.06, DMF). [g] $[\alpha]^{20}_D$ 0° (MeOH). [h] $[\alpha]^{20}_D$ +65.7° (c = 0.314, DMF). [i] $[\alpha]^{20}_D$ −63.5° (c = 0.287, DMF). [j] The trans lactam 6h and the amino ester 7d were isolated in 2.4 and 14.9% yields, respectively.

Scheme II



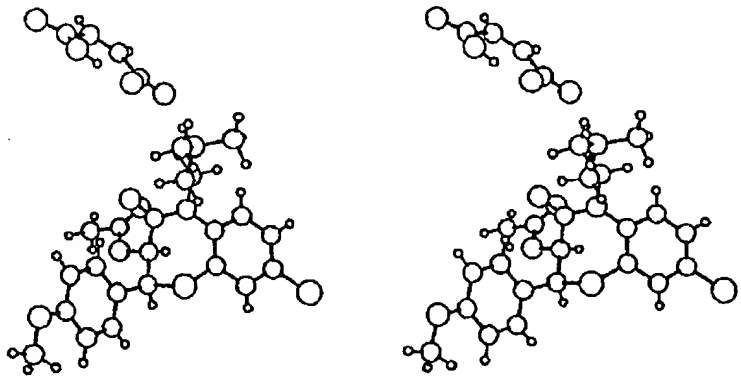


Figure 1. Stereoscopic view of (+)-2b maleate.

lective cis opening of 3-arylglycidic esters with various thiophenols.[5-7] In the presence of a catalytic amount of zinc acetate, 5- or 6-chloro-2-nitrothiophenols (14a or 14b, respectively) smoothly reacted with the 3-(4-methoxyphenyl)glycidic ester 4a at room temperature, giving the threo nitro esters 8a and 8b in good yield (Table V, method J). In the presence of $NaHCO_3$, the erythro nitro ester 9a was obtained as a sole product by trans opening of 4a (Table V).[4] The nitro esters 8 and 9 were converted to the amino acids 10 and 11 through the nitro acids 12 and 13 (Table VI, method K) or the amino ester 7 (Table III, method G).

Cyclodehydration of the amino acids 10 and 11 in boiling xylene gave the lactams 5 and 6 in good yield, respectively (Table I, method B). Treatment of the amino acid 10 with dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) also effected cyclization to give the lactam 5 (Table I, method E). Treatment of the amino ester 7 with methylsulfinyl carbanion in dimethyl sulfoxide (DMSO) easily gave the lactam 5 at room temperature (Table I, method D).

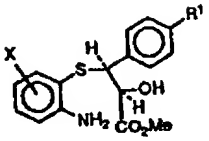
For the synthesis of optically active isomers of 5b, optical resolution of the intermediate amino acid 10a was effected with methyl L- or D-(4-hydroxyphenyl)glycinate (Table IV, method H). More practically, the nitro acid 12a could be resolved into its enantiomers via diastereoisomeric salts of L-lysine (Table VI, method L). Alternatively, optical resolution of the lactams 5e and 5k was achieved by converting them into their diastereoisomeric esters with an optically active acid. Acylation of the 3-OH group of 5e or 5k with (*S*)-*N*-(2-naphthylsulfonyl)-2-pyrrolidinecarbonyl chloride[8] gave the ester 15 as a 1:1 mixture of the diastereoisomers, which could be easily separated by column chromatography (Scheme II, method C). Alkaline hydrolysis of each diastereoisomer gave levo- and dextrorotatory isomers of the lactams 5e and 5k. Alkylation of the lactams 5 and 6 with 2-(dialkylamino)ethyl chloride in the presence of K_2CO_3 in acetone[9] (Table VII, method M) or in the presence of KOH in DMSO (Table VII, method N) gave the amino alcohol 16 (Scheme III). N Alkylation of the monomethyl derivative 17[10] gave the *N*-

Table II. Chemical Shift of the Methine Protons at C_2 and C_3 and Their Vicinal Coupling Constant in cis and trans Lactams 5 and 6 (in DMSO-d_6)

compd	chemical shift C_2-H	chemical shift C_3-H	coupling constant
	cis lactam 5		
5a	5.05	4.30	7 Hz
5b	5.10	4.37	6 Hz
5c	5.10	4.35	6.5 Hz
5d	5.08	4.44	7 Hz
5e	5.04	4.30	7 Hz
5f	5.07	4.31	6 Hz
5g	5.05	4.30	6 Hz
5h	4.78	4.32	7 Hz
5i	5.09	4.45	7 Hz
5j	5.06	4.39	7 Hz
(+)-5k	5.06	4.34	6.5 Hz
	trans lactam 6		
6a	4.41	4.09	10 Hz
6b	4.30 (s)		
6h	4.36	4.13	10 Hz
6j	4.43	4.27	13 Hz

(5) Hashiyama, T.; Inoue, H.; Konda, M.; Takeda, M. *J. Chem. Soc., Perkin Trans. 1* 1984, 1725.
(6) Hashiyama, T.; Inoue, H.; Takeda, M. *J. Chem. Soc., Perkin Trans. 1* 1985, 421.
(7) Inoue, H.; Hashiyama, T. *Japan Kokai* 1982, 57-176951; *Chem. Abstr.* 1983, *98*, 125653v.
(8) Wada, H.; Ishii, K.; Tsumagari, N.; Matsuo, M.; Matsumoto, M. *Japan Kokai* 1984, 59-76051; *Chem. Abstr.* 1984, *101*, 151603d.
(9) Gaino, M.; Iijima, I.; Nishimoto, S.; Ikeda, K.; Fujii, T. *Japan Kokai* 1983, 58-99471; Chem. Abstr. 1983, *99*, 175819v.

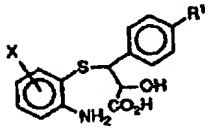
Table III. Threo Amino Esters 7



compd	X	R^1	synthetic method	yield, %	mp, °C	recryst solvent[a]	formula
7a	5-Cl	OMe	F (80 °C)	60.5	131–132	A	$C_{17}H_{16}ClNO_4S$
7b	5-Cl	Me	F (130 °C)	45	118.5–120.5	B	$C_{17}H_{16}ClNO_3S$
7c	6-Cl	OMe	G	90.2	114–116	B	$C_{17}H_{16}ClNO_4S$
7d	6-F	OMe	A	14.9[b]	110–112	C	$C_{17}H_{16}FNO_4S$
7e	3-Cl	OMe	A	16.5[c]	106.5–109.5	B	$C_{17}H_{16}ClNO_4S$

[a] A = i-Pr_2O; B = AcOEt–n-hexane; C = EtOH. [b] See footnote j in Table I. [c] See footnote c in Table I.

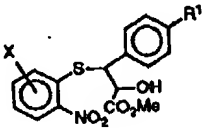
Table IV. Amino Carboxylic Acids 10 and 11



compd	X	R^1	stereoisomer	synthetic method	yield, %	mp, °C	recryst solvent[a]	formula
10a	5-Cl	OMe	threo	I	97.9	189–191	A	$C_{16}H_{16}ClNO_4S$
				G	78.8			
(+)-10a	5-Cl	OMe	threo	H	37.8[b]	176–177	B	$C_{16}H_{16}ClNO_4S$
				G	90.4			
(−)-10a	5-Cl	OMe	threo	H	35.6[c]	175–176	B	$C_{16}H_{16}ClNO_4S$
				G	70.2			
10b	5-Cl	Me	threo	I	90.5	184–185	C	$C_{16}H_{16}ClNO_3S$
10c	6-Cl	OMe	threo	I	94.8	108–110	C	$C_{16}H_{16}ClNO_4S \cdot {}^1/_2H_2O$
11a	5-Cl	OMe	erythro	G	65.6	198–198.5	D	$C_{16}H_{16}ClNO_4S$

[a] A = DMF–EtOH; B = MeOH; C = aqueous EtOH; D = DMF–i-PrOH. [b] $[\alpha]^{20}_D$ +336.5° (c = 0.376, DMF). [c] $[\alpha]^{20}_D$ −336.5° (c = 0.411, DMF).

Table V. Nitro Esters 8 and 9



compd	X	R^1	stereoisomer	catalyst	reaction conditions	yield, %	mp, °C	recryst solvent[a]	formula
8a	5-Cl	OMe	threo	$Zn(OAc)_2 \cdot 2H_2O$[b]	toluene, room temp, 3 h	71.5	141–143	A	$C_{17}H_{16}ClNO_5S$
8b	6-Cl	OMe	threo	$Zn(OAc)_2 \cdot 2H_2O$	toluene, room temp, 3 h	76.7	110–111.5	B	$C_{17}H_{16}ClNO_5S$
9a	5-Cl	OMe	erythro	$NaHCO_3$	EtOH–C_6H_6, room temp, 4 h	60.0	154–156	C	$C_{17}H_{16}ClNO_5S$

[a] A = C_6H_6–i-Pr_2O; B = AcOEt–n-hexane; C = C_6H_6. [b] The use of tin (2-ethylhexanoate)$_2$, $SnCl_4$, and $SnCl_2$ as a catalyst also gave 8a in yields of 60.0, 56.4, and 54.2%, respectively.

alkyl-N-methylamino derivatives 16d,e,i,j) (Table VII, method P).

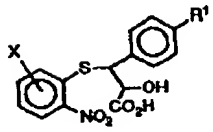
Finally, acylation or alkylation of the 3-OH group of 16 with acid anhydrides (method Q), acyl halides in pyridine (method R), n-butyl isocyanate (method S), or alkylating agents (methods T and U) gave 2 with various oxygenated functions (Table VIII).

The absolute stereochemistry of the 8-chloro derivative (+)-2b, the most interesting compound of this series, proved to be 2S,3S, by X-ray crystallographic analysis of its maleate (Figure 1). When compared with diltiazem (1) or (+)-2b, optically active isomers of the 9-chloro derivatives 5e, 16m, and 2cc showed unusually small values of specific rotation. The absolute stereochemistry of 5e and 2cc was established by comparing their ORD curves with those of the corresponding 8-chloro derivatives 5b and 2b and 1 (Figure 2).[11] Dextrorotatory series of the compounds ((+)-2b, (+)-5b, 1, and (+)-5l) exhibited high peak around 245 nm and shallow trough around 225 nm. The completely reversed ORD curves were observed for the

(10) Nakamura, S.; Sugawara, Y.; Ito, Y.; Ohtsuka, H.; Gaino, M.; Inoue, H.; Ohashi, M.; Takaichi, O. *J. Pharmacobiodynamics (Japan)*, submitted for publication.

(11) CD spectroscopic data of 1 were reported by B. Kojic-Prodic et. al.: Kojic-Prodic, B.; Ruzic-Toros, Z.; Sunjic, V.; Decorte, E.; Moimas, F. *Helv. Chim. Acta.* 1984, 67, 916.

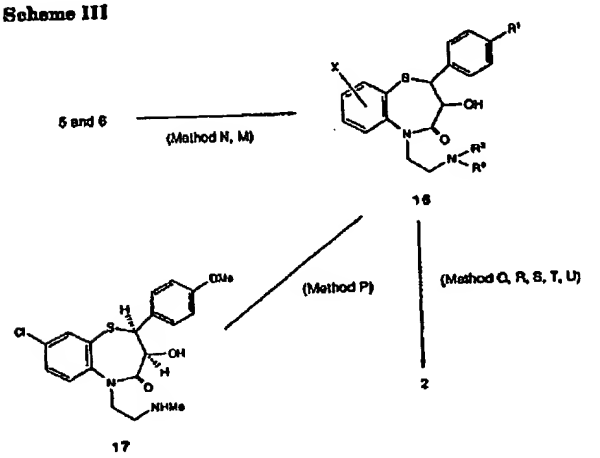
Table VI. Nitro Carboxylic Acids 12 and 13



compd	X	R^1	stereoisomer	yield, %	mp, °C	recryst solvent	formula
12a	5-Cl	OMe	threo	82.4[a]	183–186	MeOH	$C_{16}H_{14}ClNO_6S$
(+)-12a	5-Cl	OMe	threo	37.7[b]	93–97[e]	*i*-PrOH	$C_{16}H_{14}ClNO_6S$-*i*-PrOH
					124–126[d]	MeOH	$C_{16}H_{14}ClNO_6S$
(−)-12a	5-Cl	OMe	threo	30.0[b]	92–97[e]	*i*-PrOH	$C_{16}H_{14}ClNO_6S$-*i*-PrOH[f]
					123–126	MeOH	$C_{16}H_{14}ClNO_6S$
13a	5-Cl	OMe	erythro	87.6[a]	216–220	MeOH	$C_{16}H_{14}ClNO_6S$

[a] Method K. [b] Method L. [c] $[\alpha]^{20}_D$ +158.7° (c = 0.708, $CHCl_3$). [d] $[\alpha]^{20}_D$ +65.5° (c = 0.70, MeOH). [e] $[\alpha]^{20}_D$ −155.6° (c = 0.672, $CHCl_3$). [f] N: calcd, 3.16; found, 3.68.

Scheme III



corresponding levorotatory isomers (Table IX and Figure 2). These observations indicate that the absolute configuration of dextro- and levorotatory isomers are 2*S*,3*S*, and 2*R*,3*R*, respectively.

Structure–Activity Relationship

The compounds listed in Tables VII and VIII were tested for their effects on vertebral blood flow (VBF) in anesthetized dogs and coronary blood flow (CBF) in isolated guinea pig hearts and their antihypertensive activity in SHR.

The data for VBF (Table X and XI) are given in terms of the potency ratio to the effect of diltiazem after intraarterial administration. Half duration (in minutes) means the duration of one-half of maximum change in blood flow. Table X and XI also give the data for CBF. The effects are expressed as "−", if the increase in CBF is less than 0.5 mL/min at a dose of 100 μg/heart. The increase by more than 0.5 mL/min at the dose of 100, 30, 10, and 3 μg/heart is expressed as "+", "++", "+++", and "++++", respectively. The data for hypotensive activity are given as a decrease in blood pressure after oral administration of the test compound at the dose of 30 mg/kg.

Effect on Vertebral Blood Flow

Effects of the halogen substituents on the fused benzene ring of diltiazem (1) are summarized in Table X.

Introduction of a chloro substituent at the 8-position of 1 confers increased activity with longer duration of action ((+)-2b). The activity of the 7-Cl ((+)-2ll) and 9-Cl ((+)-2cc) derivatives is comparable to that of 1. In spite

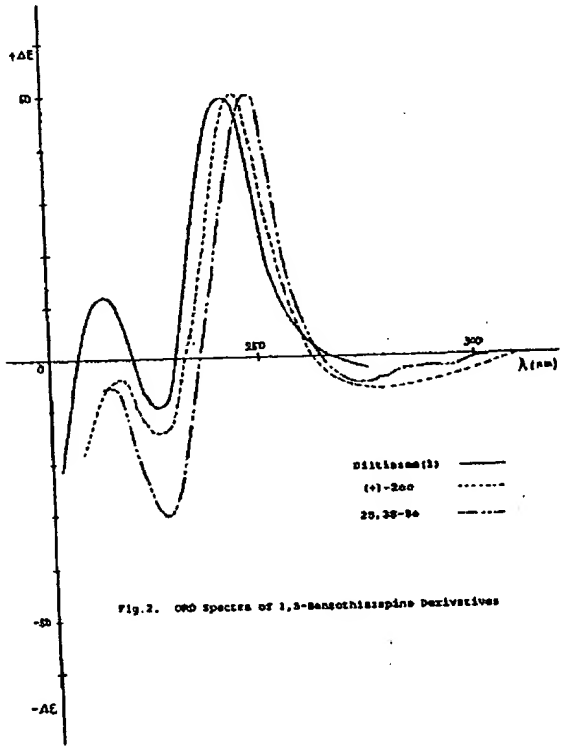
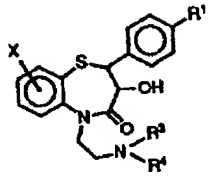


Fig.2. ORD spectra of 1,5-benzothiazepine derivatives

Figure 2. ORD spectra of 1,5-benzothiazepine derivatives.

of being racemic modifications, the 6-Cl (2a) and 7,8-Cl_2 (2jj) derivatives exhibit moderate activity. The fluoro (2dd and 2ii) and 8,9-Cl_2 (2kk) substitution result in a decrease in activity. Generally, the 3-OH derivatives are less potent than the corresponding acetoxy derivatives, except for the 9-Cl and 8,9-Cl_2 derivatives (2cc vs 16m and 2kk vs 16q). Duration of the action of the 3-OAc derivatives, however, is usually longer than that of the 3-OH derivatives. Therefore, when compared the total increase in blood flow, which is calculated by multiplying the potency ratio (maximum increase) by half duration, the 3-OAc derivatives (2cc and 2kk) are more potent than the 3-OH congeners 16m and 16q. The 2,3-trans isomer of the 8-Cl derivative (2w) and the levorotatory isomers of 2b, 2c, and 2ll are only marginally active. The importance of 2*S*,3*S* stereochemistry in this series of derivatives has already been reported.[3]

Table VII. 5-Alkylated-1,5-benzothiazepin-4(5*H*)-one Derivatives



compd	X	R^1	R^3	R^4	stereo-isomer	synthetic method	yield, %	salt	mp, °C	recryst solvent[a]	formula
16a	6-Cl	OMe	Me	Me	cis	N	55.8	HCl	230.5–231 dec	A	$C_{20}H_{23}ClN_2O_3S$·HCl
16b	8-Cl	OMe	Me	Me	cis	N	71.4	HCl	136–139	F	$C_{20}H_{23}ClN_2O_3S$·HCl·$^1/_2$EtOH
(+)-16b	8-Cl	OMe	Me	Me	cis	M	92.3	free[b]	122–124 dec	B	$C_{20}H_{23}ClN_2O_3S$
						N	73.1	oxalate[c]	201–203 dec	C	$C_{20}H_{23}ClN_2O_3S$·$C_2H_2O_4$
(−)-16b	8-Cl	OMe	Me	Me	cis	M	83.4	free[d]	121–123 dec	B	$C_{20}H_{23}ClN_2O_3S$
								oxalate[e]	202–204 dec	C	$C_{20}H_{23}ClN_2O_3S$·$C_2H_2O_4$
16c	8-Cl	OMe	Me	Me	trans	M	97.7	free	124–127	D	$C_{20}H_{23}ClN_2O_3S$
16d	8-Cl	OMe	Me	Et	cis	P	65.9	HCl	132–135 dec	A	$C_{21}H_{25}ClN_2O_3S$·HCl·$^1/_2H_2O$
						M	80.0				
(+)-16d	8-Cl	OMe	Me	Et	cis	M	84.0	$HClO_4$[f]	197–201	E	$C_{21}H_{25}ClN_2O_3S$·$HClO_4$
16e	8-Cl	OMe	Me	*n*-Pr	cis	P	60.0	HBr	82–83 dec	A	$C_{22}H_{27}ClN_2O_3S$·HBr
						M	86.0				
(+)-16f	8-Cl	OMe	Et	Et	cis	M	75.8	fumarate[g]	146–147.5	A	$C_{22}H_{27}ClN_2O_3S$·$C_4H_4O_4$
(+)-16g	8-Cl	OMe	H	H	cis	N	24.6	HCl[h]	154–157	A	$C_{18}H_{19}ClN_2O_3S$·HCl·$^1/_2H_2O$
(−)-16g	8-Cl	OMe	H	H	cis	N	11.2	HCl[i]	155–158	A	$C_{18}H_{19}ClN_2O_3S$·HCl·$^1/_2H_2O$
16h	8-Cl	OMe	Me	Bzl	cis	M	72.6	oxalate	170–173	F	$C_{28}H_{27}ClN_2O_3S$·$^1/_2C_2H_2O_4$
(+)-16h	8-Cl	OMe	Me	Bzl	cis	M	92.5	$HClO_4$[j]	161–163 dec	F	$C_{28}H_{27}ClN_2O_3S$·$HClO_4$
(−)-16h	8-Cl	OMe	Me	Bzl	cis	M	92.7	$HClO_4$[k]	161–163 dec	F	$C_{28}H_{27}ClN_2O_3S$·$HClO_4$
(+)-16i	8-Cl	OMe	Me		cis	P	77.0	fumarate[l]	136.5–138.5	A	$C_{22}H_{23}ClN_2O_3S$·$C_4H_4O_4$
(+)-16j	8-Cl	OMe	Me		cis	P	84.0	HCl[m]	195–196 dec	A	$C_{22}H_{23}ClN_2O_3S$·HCl
16k	8-Cl	SMe	Me	Me	cis	M	72.7	HCl	218–221 dec	E	$C_{20}H_{23}ClN_2O_3S_2$·HCl
16l	8-Cl	Me	Me	Me	cis	M	84.0	free	141–142	B	$C_{20}H_{23}ClN_2O_3S$
16m	9-Cl	OMe	Me	Me	cis	M	75.4	HCl	228–230 dec	E	$C_{20}H_{23}ClN_2O_3S$·HCl·H_2O
(+)-16m	9-Cl	OMe	Me	Me	cis	M	76.0	$HClO_4$[n]	190–192	E	$C_{20}H_{23}ClN_2O_3S$·$HClO_4$·$^1/_4H_2O$
(−)-16m	9-Cl	OMe	Me	Me	cis	M	87.9	$HClO_4$[o]	190–192	E	$C_{20}H_{23}ClN_2O_3S$·$HClO_4$·$^1/_4H_2O$
16n	8-F	OMe	Me	Me	cis	M	74.7	HCl	197–198	G	$C_{20}H_{23}FN_2O_3S$·HCl
16o	9-F	OMe	Me	Me	cis	M	90.2	HCl	202–205	H	$C_{20}H_{23}FN_2O_3S$·HCl
16p	7,8-Cl_2	OMe	Me	Me	cis	M	85.3	HCl	232.5–234 dec	E	$C_{20}H_{22}Cl_2N_2O_3S$·HCl[p]
16q	8,9-Cl_2	OMe	Me	Me	cis	M	45.7	HCl	230–233 dec	I	$C_{20}H_{22}Cl_2N_2O_3S$·HCl·$^3/_2H_2O$
(+)-16r	7-Cl	OMe	Me	Me	cis	M	83.9	free base[q]	92–94	J	$C_{20}H_{23}ClN_2O_3S$
(−)-16r	7-Cl	OMe	Me	Me	cis	M	86.7	free base[r]	92–94	J	$C_{20}H_{23}ClN_2O_3S$

[a] A = EtOH–Et_2O; B = AcOEt–*n*-hexane; C = EtOH–$CHCl_3$–Et_2O; D = C_6H_6; E = MeOH; F = EtOH; G = *i*-PrOH–EtOH–Et_2O; H = *i*-PrOH; I = MeOH–Et_2O; J = AcOEt–*i*-Pr_2O. [b] $[\alpha]^{20}_D$ +141.8° (*c* = 1.00, MeOH). [c] $[\alpha]^{20}_D$ +78.4° (*c* = 0.74, DMF). [d] $[\alpha]^{20}_D$ −142.7° (*c* = 1.04, MeOH). [e] $[\alpha]^{20}_D$ −78.4° (*c* = 0.88, DMF). [f] $[\alpha]^{20}_D$ +80.6° (*c* = 0.50, MeOH). [g] $[\alpha]^{20}_D$ +91.0° (*c* = 1.0, MeOH). [h] $[\alpha]^{20}_D$ +87.5° (*c* = 0.352, MeOH). [i] $[\alpha]^{20}_D$ −88.0° (*c* = 0.50, MeOH). [j] $[\alpha]^{20}_D$ +76.5° (*c* = 0.446, MeOH). [k] $[\alpha]^{20}_D$ −76.4° (*c* = 0.589, MeOH). [l] $[\alpha]^{20}_D$ +97.7° (*c* = 1.0, MeOH). [m] $[\alpha]^{20}_D$ +90.7° (*c* = 1.0, MeOH). [n] $[\alpha]^{20}_D$ +10.2° (*c* = 0.334, DMF). [o] $[\alpha]^{20}_D$ −10.3° (*c* = 0.321, DMF). [p] $[\alpha]^{20}_D$ +126.7° (*c* = 0.390, MeOH). [q] $[\alpha]^{20}_D$ −126.3° (*c* = 0.437, MeOH). [r] C: calcd, 53.17; found, 52.72. [s] C: calcd, 50.94; found, 50.40. [t] C: calcd, 50.94; found, 50.49. [u] Cl: calcd, 22.26; found, 22.90.

In view of the good activity of the 8-Cl derivative (2b), the effect of modifying the substituents at the 2, 3, and 5 position was further examined (Table XI). With regard to the effect of the length of the 3-acyloxy group on activity, maximum activity is seen in the acetoxy (2b) and propionyloxy (2d) derivatives. Gradual decrease in activity is observed with the lower (2c) or higher (2e and 2f) analogues. The methoxy (2m), carbamate (2g), carbonate (2h), and various benzoyl (2i–l) derivatives exhibit decreased activity.

When the dimethylamino group in the side chain of 2b is replaced by larger amino groups (2o–u), a significant decrease in potency is observed. Only the methylallylamino derivative (2r) exhibits good potency with short duration of action.

Replacement of the 4-MeO group in the 2-phenyl moiety of 2b with MeS (2bb) and Me (2x) groups results in a considerable decrease in activity.

Effect on Coronary Blood Flow

The most effective compounds in this test are (+)-2e, (+)-2f, (+)-2cc, (±)-2hh, and (+)-2p. They increase CBF by more than 0.5 mL/min even at the dose of 3 μg/heart. No clear relationships are observed between the effects on CBF and VBF (Tables X and XI).

Hypotensive Effect in SHR

Some of the compounds showed interesting effects on VBF and CBF were tested for their hypotensive activity in SHR (Table XII). The hypotensive activity of the compounds is roughly parallel with their effect on VBF. Thus, the 3-acyloxy derivatives ((+)-2b, (+)-2cc, (+)-2o, (+)-2c, and (+)-2d) with strong increasing effect on VBF (Tables X and XI) exhibit long-lasting and potent hypotensive action. The most active compound in this series, (+)-2b, was found to be 3 or 4 times as potent as diltiazem. The corresponding carbinols ((+)-16b, (±)-16d, and (+)-16m) of these *o*-acyl derivatives exhibit much-reduced activity. Compounds (+)-2m, 2dd, and 2ii show good activity in spite of their moderate effect on VBF.

As a consequence of the above SAR, (+)-(2*S*,3*S*)-3-acetoxy-8-chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one ((+)-2b) was selected for further study. The maleate of (+)-2b is currently under clinical trial as a cerebral vasodilating and antihypertensive agent under the code name

of TA-3090.[12] Some pharmacological profiles of TA-3090 have been reported in separate papers.[13]

Experimental Section

The reaction of the nitro- or aminothiophenols with glycidic ester was carried out under argon atmosphere. Melting points were determined on a Yamato melting point apparatus Model MP-12 and are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained on JEOL PMX-60, Hitachi RH-90H, or JEOL FX-200 spectrometer. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (Me_4Si: 0.0) as an internal standard.

Coupling constants (J) are reported in hertz (Hz), and s, d, t, q, m, and bs refer to singlet, doublet, triplet, quartet, multiplet, and broad singlet, respectively. Infrared spectra (IR) were recorded on a Hitachi IR-215 spectrophotometer. ORD curves were recorded on a JASCO J-20A spectropolarimeter at room temperature. The organic solutions were dried over Na_2SO_4, and all evaporations were carried out in vacuo. Analytical data of the compounds listed in the tables are within ±0.4% of the theoretical values unless otherwise noted.

Halogen-Substituted 2-Aminothiophenol (3). 4-Chloro-, 6-chloro-, 5,6-dichloro, 6,7-dichloro, and 6-fluoro-2-aminobenzothiazoles were prepared by the method described in the literatures.[14] 7-Fluoro-2-aminobenzothiazole was prepared by the action of potassium thiocyanate and bromine on *m*-fluoroaniline in the same manner reported in ref 14 in 72% yield: mp 174–175 °C (from *i*-PrOH); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 6.75 (dd, J = 9 and 3 Hz, 1 H), 7.11 (dd, J = 11 and 3 Hz, 1 H), 7.62 (s, 2 H, NH_2), 7.63 (dd, J = 9 and 11 Hz, 1 H). Anal. ($C_7H_5FN_2S$) C, H, N, S.

A mixture of 2-aminobenzothiazoles (50 g), sodium hydroxide (150 g), and water (300 mL) was heated under reflux for 15–24 h under Ar atmosphere. The reaction mixture was diluted with ice–water, neutralized with dilute HCl under cooling to adjust pH 3–4, and extracted with toluene. The extracts were combined, washed with saturated aqueous NaCl, and concentrated to give the substituted 2-aminothiophenols as a yellow oil (X = 5-Cl (80–90%), 3-Cl (90%), 5-F (75.5%), 6-F (93.4%), 5,6-Cl_2 (99.5%), and 4,5-Cl_2 (92.9%), which were used for the next step without further purification.

(±)-*cis*-8-Chloro-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (5b). Method A. A mixture of 2-amino-5-chlorothiophenol (20.3 g, 0.127 mol) and 4a (26.4 g, 0.129 mol) was heated at 160 °C for 16 h. After cooling, the reaction mixture was triturated with small amount of EtOH and recrystallized from AcOEt–*n*-hexane to give 11.3 g of the cis lactam 5b, mp 230–232 °C.

The mother liquor was concentrated, dissolved in AcOEt, washed with 10% HCl and water, dried, and concentrated. The residual oil was separated by silica gel column chromatography (eluted with $CHCl_3$). From the first eluate, additional amount of 5b (770 mg) was obtained (total yield, 28.3%): IR (Nujol) 3350, 3180, 3100, 1680 cm^{-1}; EIMS m/z 335; ^{1}H NMR (DMSO-d_6, 90 MHz) δ 3.78 (s, 3 H), 5.10 (d, J = 6 Hz, 1 H, 2-H), 4.37 (t, J = 6 Hz, 1 H, 3-H), 4.83 (d, J = 8 Hz, 2 H, Ar H), 7.2–7.7 (m, 5 H, Ar H). Anal. ($C_{16}H_{14}ClNO_3S$) C, H, N, Cl.

The trans lactam 6b (1.66 g, 3.9%), mp 183–185 °C (from AcOEt–*n*-hexane), was obtained from the second eluate: IR (Nujol) 3490, 3190, 3090, 1685 cm^{-1}; EIMS m/z 335; ^{1}H NMR (DMSO-d_6, 90 MHz) δ 3.78 (s, 3 H), 4.30 (s, 2 H, 2,3-H), 6.86 (d, J = 8.6 Hz, 2 H, Ar H); 7.1–7.6 (m, 5 H, Ar H). Anal. ($C_{16}H_{14}ClNO_3S$) C, H, N, Cl.

Cyclization of the Amino Acid 10a. Method B. (±)-*threo*-3-[(2-Amino-5-chlorophenyl)thio]-2-hydroxy-3-(4-methoxyphenyl)propionic acid (10a) (8.0 g, 22.6 mmol) was heated in xylene (600 mL) under reflux for 24 h. After cooling, the precipitated needles were collected, washed with Et_2O, and recrystallized from AcOEt–*n*-hexane to give 6.1 g (80.3%) of 5b, mp 230–232 °C.

Optical Resolution of the Lactam 5a. Method C. (i) (*S*)-*N*-(2-Naphthylsulfonyl)-2-pyrrolidinecarbonyl chloride[8] (28.4 g, 87.7 mmol) was added to a suspension of 5e (22.39 g, 66.7 mmol) in pyridine (60 mL) at 5–15 °C, and the mixture was stirred at room temperature for 18 h.

After dilution of the mixture with AcOEt–$CHCl_3$ (1:1) and water, the organic layer was separated, washed with 10% HCl, water, aqueous 5% $NaHCO_3$, and water, successively, dried, and concentrated. The residual oil was separated by flash column chromatography (silica gel, eluted with C_6H_6–AcOEt (9:1)).

From the first fraction, 2*S*,3*S*-15a (18.22 g, 43.9%) was obtained as an oil: $[\alpha]^{20}_D$ −113.2° (c = 0.326, $CHCl_3$); IR (film) 3300, 3200–3000, 1745, 1690 cm^{-1}; EIMS, m/z 622, 319, 317, 286, 284; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.2–2.0 (m, 4 H), 3.12 (t, J = 6 Hz, 2 H), 3.78 (s, 3 H, OCH_3), 4.23 (t, J = 5 Hz, 1 H), 4.76 (d, J = 8 Hz, 1 H), 4.96 (d, J = 8 Hz, 1 H), 6.7–8.7 (m, 14 H).

From the second fraction, 2*R*,3*R*-15a (17.01 g, 39.3%) was obtained: mp 106–123 °C (from benzene); $[\alpha]^{20}_D$ +22.8° (c = 0.324, $CHCl_3$); IR (Nujol) 3200–3000, 1760, 1680 cm^{-1}; EIMS m/z 622, 319, 317, 286, 284; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.5–1.9 (m, 4 H), 3.30 (m, 2 H), 3.79 (s, 3 H, OCH_3), 4.20 (bt, 1 H), 5.22 (d, J = 8 Hz, 1 H), 5.26 (d, J = 8 Hz, 1 H), 6.8–8.7 (m, 14 H). Anal. ($C_{31}H_{27}ClN_2O_6S_2 \cdot {}^3/_2H_2O$) C, H, N, S, Cl.

(ii) 2*S*,3*S*-15a (17.46 g, 28.02 mmol) was hydrolyzed by stirring in a solution of K_2CO_3 (41 g) in H_2O–MeOH (1:2) (300 mL) at room temperature for 19 h. The reaction mixture was diluted with water, and the precipitated crystals were collected and recrystallized from MeOH–H_2O to give 7.85 g (83.4%) of 2*S*,3*S*-5e: mp 187–189 °C; $[\alpha]^{20}_D$ 0° (c = 0.275, DMF); IR (Nujol) 3350, 3160, 3100 (NH_2, OH), 1680, 1630, 1600 cm^{-1}; ^{1}H NMR (DMSO-d_6, 60 MHz) δ 3.79 (s, 3 H, OCH_3), 4.32 (bt, 1 H, 3-H), 4.88 (bd, J = 6 Hz, 1 H, OH), 5.09 (d, J = 7 Hz, 1 H, 2-H), 6.8–7.6 (m, 7 H). Anal. ($C_{16}H_{14}ClNO_3S$) C, H, N, S, Cl.

2*R*,3*R*-5e, mp 188–189 °C (from aqueous MeOH), was also obtained in 91.3% yield from 2*R*,3*R*-15a in the same manner described above: $[\alpha]^{20}_D$ 0° (c = 0.275, DMF); IR and ^{1}H NMR (DMSO-d_6) spectra were superimposable over those of the 2*S*,3*S*-5e. Anal. ($C_{16}H_{14}ClNO_3S$) C, H, N, S, Cl.

(±)-*cis*-9-Fluoro-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (5h). Method D. Under Ar atmosphere and ice cooling, a solution of the amino ester 7d (3.0 g, 8.55 mmol) in DMSO (7 mL) was added to a solution of dimethylsulfinylcarbanion in DMSO (prepared from 63% NaH (dispersion in mineral oil, 683 mg, 18 mmol) and DMSO (12 mL)). After being stirred at room temperature for 5 min, the reaction mixture was poured into a mixture of cracked ice and AcOH (0.2 mL) and the precipitated crystals were collected and recrystallized from DMF–EtOH to give 2.39 g (87.7%) of 5h: mp 218–222 °C; IR (Nujol) 3380, 3230, 1680 cm^{-1}; ^{1}H NMR (DMSO-d_6, 60 MHz) δ 3.31 (s, 3 H, OCH_3), 4.78 (d, J = 7 Hz, 1 H, 2-H), 4.32 (t, J = 7 Hz, 1 H, 3-H), 6.8–7.8 (m, 7 H), 4.7 (d, J = 7 Hz, 1 H, OH). Anal. ($C_{16}H_{14}FNO_3S$) C, H, N, S, F.

(2*R*,3*R*)-9-Chloro-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (2*R*,3*R*-5e). Method E. To a mixture of (−)-10c[15] (600 mg, 1.70 mmol), HOBt (150 mg), CH_2Cl_2 (5 mL), and DMF (2 mL) was added DCC (550 mg, 2.67 mmol), and the mixture was stirred at room temperature for 18 h. Small amount of water was added to the reaction mixture and dicyclohexylurea was filtered off. The mother liquor was concentrated. The residual oil was dissolved in AcOEt, washed with 5% $NaHCO_3$, dried, and concentrated. The residue was recrystallized from aqueous MeOH to give 414 mg (72.6%) of 2*R*,3*R*-5e, mp 188–189 °C.

Methyl *threo*-3-[(2-Amino-5-chlorophenyl)thio]-2-hydroxy-3-(4-methoxyphenyl)propionate (7a). Method F. A mixture of 2-amino-5-chlorothiophenol (3c) (198 g, 1.24 mol)

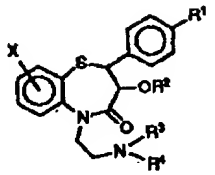
(12) The proposed INN is clentiazem.

(13) Narita, H.; Murata, S.; Yabana, H.; Kikkawa, K.; Akimoto, Y.; Nagao, T. *Arzneim-Forsch./Drug Res.* 1988, *38*, 515. Murata, S.; Kikkawa, K.; Yabana, H.; Nagao, T. *Arzneim-Forsch./Drug Res.* 1988, *38*, 521. Kikkawa, K.; Murata, S.; Nagao, T. *Arzneim-Forsch./Drug Res.* 1988, *38*, 526.

(14) For the 4-Cl and 6-Cl derivatives: Mital, R. L.; Jain, S. K. *J. Chem. Soc. (C)* 1969, 2148. Gupta, R. R.; Ojha, K. G.; Kumar, M. *J. Heterocyclic Chem.* 1980, *17*, 1375. For the 5,6-Cl_2 and 6,7-Cl_2 derivatives: Alamino, R. J. *J. Heterocyclic Chem.* 1971, *8*, 309. For the 6-F derivative: Papke, K.; Pohloudek-Fabini, R. *Pharmazie* 1967, *22*, 229.

(15) (−)-10c was obtained as a byproduct in hydrolysis of 2*R*,3*R*-15a with 5% aqueous NaOH–MeOH at room temperature.

Table VIII. Physicochemical Data for 2



compd	X	R^1	R^2	R^3	R^4	stereo-isomer	syn-thetic method	yield, %	salt	mp, °C	recryst solvent[a]	formula
2a	6-Cl	OMe	Ac	Me	Me	cis	Q	81.6	HCl	246–248.5 dec	A	$C_{22}H_{25}ClN_2O_4S$·HCl
2b	8-Cl	OMe	Ac	Me	Me	cis	Q	80.0	HCl	159–161	B	$C_{22}H_{25}ClN_2O_4S$·HCl·EtOH
(+)-2b	8-Cl	OMe	Ac	Me	Me	cis	Q	90.9	HCl	128–132 dec[b]	C	$C_{22}H_{25}ClN_2O_4S$·HCl·$^1/_2H_2O$
									maleate	160.5–161.5[c]	F	$C_{22}H_{25}ClN_2O_4S$·$C_4H_4O_4$
(−)-2b	8-Cl	OMe	Ac	Me	Me	cis	Q	82.2	HCl	127–131 dec[d]	C	$C_{22}H_{25}ClN_2O_4S$·HCl·$^1/_2H_2O$
									maleate	160.5–161.5[e]	F	$C_{22}H_{25}ClN_2O_4S$·$C_4H_4O_4$
(+)-2c	8-Cl	OMe	CHO	Me	Me	cis	Q	67.0	oxalate	180–183 dec[f]	D	$C_{21}H_{23}ClN_2O_4S$·$C_2H_2O_4$
(+)-2d	8-Cl	OMe	COEt	Me	Me	cis	R	97.5	oxalate	166–169[g]	E	$C_{23}H_{27}ClN_2O_4S$·$C_2H_2O_4$
(+)-2e	8-Cl	OMe	CO*n*-Pr	Me	Me	cis	R	97.0	oxalate	140–142[h]	F	$C_{24}H_{29}ClN_2O_4S$·$C_2H_2O_4$
(+)-2f	8-Cl	OMe	CO*n*-Bu	Me	Me	cis	R	94.8	oxalate	167–169[i]	F	$C_{25}H_{31}ClN_2O_4S$·$C_2H_2O_4$
2g	8-Cl	OMe	CONH*n*-Bu	Me	Me	cis	S	85.6	HCl	142–144 dec	B	$C_{26}H_{32}ClN_3O_4S$·HCl
2h	8-Cl	OMe	CO_2Et	Me	Me	cis	R	65.5	HCl	164–166 dec	D	$C_{24}H_{27}ClN_2O_6S$·HCl·$^1/_2H_2O$
2i	8-Cl	OMe	4-NO_2Bz[j]	Me	Me	cis	R	96.2	free	173–175 dec	G	$C_{27}H_{26}ClN_3O_6S$
(+)-2j	8-Cl	OMe	4-NO_2-2-ClBz	Me	Me	cis	R	*q*	oxalate	194–197[j]	B	$C_{27}H_{25}Cl_2N_3O_6S$·$C_2H_2O_4$
(+)-2k	8-Cl	OMe	4-Cl-3-NO_2Bz	Me	Me	cis	R	100	fumarate	124.5–126[k]	A	$C_{27}H_{25}Cl_2N_3O_6S$·$C_4H_4O_4$·$^1/_3$MeOH·H_2O
2l	8-Cl	OMe	4-MeBz	Me	Me	cis	R	46.0	oxalate	196–198 dec	F	$C_{28}H_{29}ClN_2O_4S$·$C_2H_2O_4$·EtOH
(+)-2m	8-Cl	OMe	Me	Me	Me	cis	T	61.5	HCl	245–248[l]	H	$C_{21}H_{23}ClN_2O_4S$·HCl
(+)-2n	8-Cl	OMe	4-NO_2Bz[l]	Me	Me	cis	U	17.0	oxalate	99.5–109[m]	I	$C_{27}H_{25}ClN_4O_8S$·$C_2H_2O_4$·$^2/_3$EtOH·$^1/_3$*i*-PrOH
2o	8-Cl	OMe	Ac	Me	Et	cis	Q	91.5	HCl	229–232 dec	B	$C_{23}H_{27}ClN_2O_4S$·HCl·$^1/_2H_2O$
(+)-2o	8-Cl	OMe	Ac	Me	Et	cis	Q	88.6	L-tartrate	128–133 dec[n]	F	$C_{23}H_{27}ClN_2O_4S$·$C_4H_6O_6$
(+)-2p	8-Cl	OMe	Me	Me	Et	cis	T	64.0	fumarate	172–173[o]	J	$C_{22}H_{27}ClN_2O_4S$·$C_4H_4O_4$
2q	8-Cl	OMe	Ac	Me	*n*-Pr	cis	Q	70.0	oxalate	197–198 dec	B	$C_{24}H_{29}ClN_2O_4S$·$C_2H_2O_4$
(+)-2r	8-Cl	OMe	Ac	Me		cis	Q	86.0	oxalate	172.5–174.5[p]	F	$C_{24}H_{27}ClN_2O_4S$·$C_2H_2O_4$
(+)-2s	8-Cl	OMe	Ac	Me		cis	Q	48.0	oxalate	133–136[q]	D	$C_{24}H_{25}ClN_2O_4S$·$C_2H_2O_4$
2t	8-Cl	OMe	Ac	Me	Bzl	cis	Q	55.1	HCl	225–228 dec	B	$C_{28}H_{29}ClN_2O_4S$·HCl·H_2O
(−)-2t	8-Cl	OMe	Ac	Me	Bzl	cis	Q	100	oxalate	192–194[r]	F	$C_{29}H_{29}ClN_2O_4S$·$C_2H_2O_4$
(+)-2t	8-Cl	OMe	Ac	Me	Bzl	cis	Q	100	free	oil		
(+)-2u	8-Cl	OMe	Ac	Et	Et	cis	Q	85.8	oxalate	183–184.5 dec[s]	F	$C_{24}H_{27}ClN_2O_4S$·$C_2H_2O_4$
(+)-2v	8-Cl	OMe	Ac	H	H	cis	R	44.8	fumarate	158–162 dec[t]	D	$C_{20}H_{21}ClN_2O_4S$·$C_4H_4O_4$·$^3/_4H_2O$
(−)-2v	8-Cl	OMe	Ac	H	H	cis	R	36.0	fumarate	157–160 dec[u]	D	$C_{20}H_{21}ClN_2O_4S$·$C_4H_4O_4$·$^3/_4H_2O$
2w	8-Cl	OMe	Ac	Me	Me	trans	Q	95.0	HCl	231–233 dec	H	$C_{22}H_{25}ClN_2O_4S$·HCl
									oxalate	197–199	A	$C_{22}H_{25}ClN_2O_4S$·$C_2H_2O_4$
2x	8-Cl	Me	Ac	Me	Me	cis	Q	69.0	HCl	131–135	I	$C_{21}H_{23}ClN_2O_3S$·HCl·$^1/_2$EtOH·$^1/_2H_2O$[w]
2y	8-Cl	Me	4-NO_2Bz	Me	Me	cis	R	56.0	HCl	218–220.5	D	$C_{27}H_{24}ClN_3O_5S$·HCl·H_2O
2z	8-Cl	Me	4-NO_2-2-ClBz	Me	Me	cis	R	64	HCl	174.5–177.5	D	$C_{27}H_{23}Cl_2N_3O_5S$·HCl·H_2O
2aa	8-Cl	Me	4-Cl-2-NO_2Bz	Me	Me	cis	R	74	HCl	168–170	D	$C_{27}H_{23}Cl_2N_3O_5S$·HCl·$^1/_2$EtOH
2bb	8-Cl	SMe	Ac	Me	Me	cis	Q	88.9	HCl	136–139 dec	J	$C_{23}H_{27}ClN_2O_3S_2$·HCl·*i*-PrOH
2cc	9-Cl	OMe	Ac	Me	Me	cis	Q	89.4	HCl	185–189 dec	H	$C_{23}H_{27}ClN_2O_4S$·HCl·H_2O
(+)-2cc	9-Cl	OMe	Ac	Me	Me	cis	Q	88.9	HCl	140–143[x]	D	$C_{23}H_{27}ClN_2O_4S$·HCl·H_2O
(−)-2cc	9-Cl	OMe	Ac	Me	Me	cis	Q	89.8	HCl	139–142[w]	D	$C_{23}H_{27}ClN_2O_4S$·HCl·H_2O
2dd	8-F	OMe	Ac	Me	Me	cis	Q	87.3	HCl	137–141	D	$C_{22}H_{25}FN_2O_4S$·HCl·$^1/_2H_2O$
2ee	8-F	OMe	CONH*n*-Bu	Me	Me	cis	S	87.0	HCl	110–113 dec	K	$C_{26}H_{32}FN_3O_4S$·HCl
2ff	8-F	OMe	CO_2Et	Me	Me	cis	R	79.8	HCl	135–138 dec	K	$C_{24}H_{27}FN_2O_6S$·HCl·*i*-PrOH
2gg	8-F	OMe	4-NO_2Bz	Me	Me	cis	R	59.8	$^1/_2$oxalate	213–214 dec	L	$C_{27}H_{26}FN_3O_6S$·$^1/_2C_2H_2O_4$·$^1/_2H_2O$
2hh	8-F	OMe	4-MeBz	Me	Me	cis	R	56.0	$^1/_2$oxalate	197–198 dec	L	$C_{28}H_{29}FN_2O_4S$·$^1/_2C_2H_2O_4$·$2H_2O$[bb]
2ii	9-F	OMe	Ac	Me	Me	cis	Q	66.4	HCl	200–204 dec	K	$C_{22}H_{25}FN_2O_4S$·HCl
2jj	7,8-Cl_2	OMe	Ac	Me	Me	cis	Q	85.3	HCl	189–192 dec	A	$C_{23}H_{24}Cl_2N_2O_4S$·HCl
2kk	8,9-Cl_2	OMe	Ac	Me	Me	cis	Q	85.1	HCl	233–235 dec	D	$C_{23}H_{24}Cl_2N_2O_4S$·HCl·$^1/_2H_2O$
(+)-2ll	7-Cl	OMe	Ac	Me	Me	cis	Q	85.5	HCl	162–164[y]	H	$C_{22}H_{25}ClN_2O_4S$·HCl
(−)-2ll	7-Cl	OMe	Ac	Me	Me	cis	Q	76.2	HCl	163–165[y]	H	$C_{22}H_{25}ClN_2O_4S$·HCl

Footnotes to Table VIII

[a] A = MeOH; B = EtOH–$CHCl_3$–Et_2O; C = EtOH–acetone; D = EtOH–Et_2O; E = acetone; F = EtOH; G = AcOEt–*n*-hexane; H = MeOH–Et_2O; I = EtOH–*i*-PrOH; J = *i*-PrOH; K = *i*-PrOH–Et_2O; L = DMF–EtOH. [b] $[\alpha]^{20}_D$ +92.2° (*c* = 0.796, EtOH). [c] $[\alpha]^{20}_D$ +76.5° (*c* = 1.00, MeOH). [d] $[\alpha]^{20}_D$ −93.3° (*c* = 0.872, EtOH). [e] $[\alpha]^{20}_D$ −76.8° (*c* = 1.00, MeOH) (maleate). [f] $[\alpha]^{20}_D$ +117.8° (*c* = 1.0, DMF). [g] $[\alpha]^{20}_D$ +65.3° (*c* = 0.248, MeOH). [h] $[\alpha]^{20}_D$ +61.3° (*c* = 0.320, MeOH). [i] $[\alpha]^{20}_D$ +56.4° (*c* = 0.328, MeOH). [j] $[\alpha]^{20}_D$ +32.0° (*c* = 1.0, DMF). [k] $[\alpha]^{20}_D$ + 15.8° (*c* = 0.60, MeOH). [l] $[\alpha]^{20}_D$ +60.7° (*c* = 0.287, MeOH). [m] $[\alpha]^{20}_D$ −16.9° (*c* = 0.630, MeOH). [n] $[\alpha]^{20}_D$ +84.0° (*c* = 1.0, MeOH). [o] $[\alpha]^{20}_D$ +69.7° (*c* = 0.52, DMF). [p] $[\alpha]^{20}_D$ +83.2° (*c* = 1.0, MeOH). [q] $[\alpha]^{20}_D$ +84.4° (*c* = 1.0, MeOH). [r] $[\alpha]^{20}_D$ −96.5° (*c* = 1.0, MeOH). [s] $[\alpha]^{20}_D$ +86.6° (*c* = 1.0, MeOH). [t] $[\alpha]^{20}_D$ +68.3° (*c* = 0.250, MeOH). [u] $[\alpha]^{20}_D$ −66.5° (*c* = 0.40, MeOH). [v] $[\alpha]^{20}_D$ +13.0° (*c* = 0.347, MeOH). [w] $[\alpha]^{20}_D$ −13.0° (*c* = 0.348, MeOH). [x] $[\alpha]^{20}_D$ +83.1° (*c* = 0.355, MeOH). [y] $[\alpha]^{20}_D$ −82.8° (*c* = 0.331, MeOH). [z] Bz = benzoyl; Bzl = benzyl. [aa] Cl: calcd, 14.14; found, 14.64. [bb] S: calcd, 5.44; found, 5.94.

Table IX. ORD Data for 1,5-Benzothiazepine Derivatives (5×10^{-4} mol in MeOH)

compd	λ_{max}, nm	[θ]
diltiazem (1)	214	+45 300
	226	−32 900
	243	+162 600
	274	−4 100
(−)-isomer of 1	214	−51 000
	224	+30 600
	243	−163 300
	274	+6 800
(+)-2b maleate	216	+20 100
	226	−46 900
	247	+198 400
(−)-2b maleate	216	−22 700
	226	+45 500
	247	−199 600
(+)-2cc·HCl·H_2O	217	−12 300
	226	−48 300
	246	+166 000
	280	−22 600
(−)-2cc·HCl·H_2O	217	+11 900
	226	+50 700
	246	−176 000
	280	+23 100
2*S*,3*S*-5e	227	−100 000
	249	+165 000
	275	−19 100
2*R*,3*R*-5e	227	+101 000
	249	−170 000
	275	+18 900
(+)-5l (X = H, R^1 = OMe)	223	−69 400
	243	+154 000
	270	+5 900
(−)-5l	223	+70 300
	243	−161 000
	270	−6 460

and 4a (258 g, 1.24 mol) in toluene (1.9 L) was stirred at 80 °C for 24 h and cooled. The precipitated needles were collected and recrystallized from *i*-Pr_2O to give 276 g (60.5%) of 7a: mp 131–132 °C; IR (Nujol) 3530, 3430, 3340, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 3.62 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.49 (m, 2 H, methine H), 6.8–7.8 (m, 7 H). Anal. ($C_{17}H_{18}ClNO_4S$) C, H, N, S, Cl.

Methyl *threo*-3-[(2-Amino-6-chlorophenyl)thio]-2-hydroxy-3-(4-methoxyphenyl)propionate (7c). Method G. The threo nitro ester (8b) (62 g, 0.156 mol) was hydrogenated in AcOH (500 mL) and EtOH (500 mL) in the presence of 10% Pd–C (7.0 g) under ordinary pressure at room temperature for 11 h. The reaction mixture was worked up in the usual manner to give 51.74 g (90.2%) of 7c: mp 114–116 °C; IR (Nujol) 3500, 3325, 3200, 1745 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 3.53 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.58 (bs, 4 H, 2-H, OH, NH_2), 4.82 (d, *J* = 3 Hz, 1 H, 3-H), 6.85 (d, *J* = 9 Hz, 2 H), 7.49 (d, *J* = 9 Hz, 2 H), 6.3–7.6 (m, 3 H). Anal. ($C_{17}H_{18}ClNO_4S$) C, H, N, S, Cl.

Optical Resolution of the Amino Acid 10a. Method H. A solution of 97% KOH (10.7 g, 0.191 mol) in MeOH (100 mL) was added to a solution of methyl L-(4-hydroxyphenyl)glycinate hydrochloride (41.56 g, 0.191 mol) in MeOH (1.4 L) under ice cooling and KCl was filtered off. The amino acid 10a (40 g, 0.113 mol) was added to the filtrate, and the mixture was concentrated below 50 °C. The residue was diluted with EtOH (200 mL) and allowed to stand at 4 °C. The precipitated needles were collected and washed with a small amount of cold EtOH. The needles were dissolved in EtOH (1 L) at 70 °C, concentrated below 60 °C until the volume of the solution became about 250 mL, and the precipitated crystals were collected. This recrystallization procedure was repeated again to give (+)-10a methyl L-(4-hydroxyphenyl)glycinate salt (28.42 g, 47.0%): mp 168–171 °C; $[\alpha]^{20}_D$ +310.7° (*c* = 0.360, DMF); IR (Nujol) 3330, 3280, 2800–2200, 1735, 1610 cm^{-1}. Anal. ($C_{16}H_{18}ClNO_4S$·$C_9H_{11}NO_3$) C, H, N, Cl.[16]

The salt (62.63 g, 117 mmol) was dissolved in 10% HCl (100 mL) and diluted with water (1 L). The precipitated white needles were collected and recrystallized from MeOH to give 33.32 g (80.5%) of (+)-10a: mp 176–177 °C; $[\alpha]^{20}_D$ +336.5° (*c* = 0.376, DMF), +320° (*c* = 0.730, MeOH); IR (Nujol) 3520, 3450, 3350, 1730, 1680, 1610 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.71 (s, 3 H, OCH_3), 4.29 (d, *J* = 5.7 Hz, 1 H), 4.36 (d, *J* = 5.7 Hz, 1 H), 6.6–7.3 (m, 7 H).

The mother liquors of the salt of (+)-10a were combined, concentrated, and made acidic in the same manner as described above. Fractional recrystallization of the precipitates from MeOH gave (−)-10a (29.94 g, 35.6%): mp 175–176 °C; $[\alpha]^{20}_D$ −335.5% (*c* = 0.411, DMF) and (±)-10a (13.1 g, mp 189–191 °C). IR and NMR spectra of (−)-10a were superimposable over those of (+)-10a.

Hydrolysis of the Amino Ester 7a. Method I. A mixture of the amino ester 7a (332 g, 0.903 mol), 5% aqueous NaOH (3.3 L), and EtOH (3.3 L) was stirred at room temperature for 3 h and neutralized with dilute HCl (pH 4–5), and the crystalline product was filtered. Recrystallization from DMF–EtOH gave 312.8 g (97.9%) of 10a: mp 189–191 °C; IR (Nujol) 3290, 2800–2200, 1610, 1580, 1560, 1510 cm^{-1}; ^1H NMR (DMSO-d_6, 90 MHz) δ 3.71 (s, 3 H, OCH_3), 4.29 (d, *J* = 6.3 Hz, 1 H), 4.36 (d, *J* = 6.3 Hz, 1 H), 6.6–7.3 (m, 7 H). Anal. ($C_{16}H_{16}ClNO_4S$) C, H, N, S, Cl.

Methyl *threo*-3-[(5-Chloro-2-nitrophenyl)thio]-2-hydroxy-3-(4-methoxyphenyl)propionate (8a). Method J. 4a (2.38 g, 11.4 mmol) was added to a mixture of 5-chloro-2-nitrothiophenol[17] (1.68 g, 8.97 mmol) and $Zn(OAc)_2$·$2H_2O$ (30 mg, 0.137 mmol) in toluene (17 mL). The reaction mixture was stirred at room temperature for 3 h and concentrated. The residual solid was washed with *i*-Pr_2O and recrystallized from C_6H_6–*i*-Pr_2O to give 2.55 g (71.5%) of 8a: mp 141–143 °C as yellow needles; IR (Nujol) 3490, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 3.26 (d, *J* = 5 Hz, OH), 3.77 (s, 6 H, OCH_3), 4.59 (dd, *J* = 3 and 5 Hz, 2-H), 4.69 (d, *J* = 3 Hz, 1 H, 3-H), 6.84 (d, *J* = 9 Hz, 2 H), 7.43 (d, *J* = 9 Hz, 2 H), 7.95 (d, *J* = 9 Hz, 1 H), 7.0–7.5 (m, 2 H). Anal. ($C_{17}H_{16}ClNO_6S$) C, H, N, S, Cl.

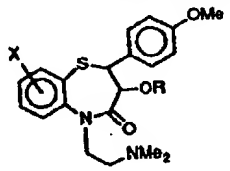
Hydrolysis of the Nitro Ester 8a. Method K. A mixture of the nitro ester 8a (22.0 g, 55.3 mmol), 10% NaOH (120 mL), and MeOH (400 mL) was stirred at room temperature for 8 h. The reaction mixture was acidified with concentrated HCl and filtered. Recrystallization from MeOH gave 17.49 g (82.4%) of 12a: mp 183–186 °C as yellow plates; IR (Nujol) 3540, 3300–2000, 1720, 1610, 1590 cm^{-1}; ^1H NMR (DMSO-d_6, 90 MHz) δ 3.72 (s, 3 H, OCH_3), 4.35 (d, *J* = 5 Hz, 1 H), 4.97 (d, *J* = 5 Hz, 1 H), 6.87 (d, *J* = 9 Hz, 2 H), 7.46 (d, *J* = 9 Hz, 2 H), 7.3–7.7 (m, 2 H), 8.05 (d, *J* = 8.8 Hz, 1 H). Anal. ($C_{16}H_{14}ClNO_6S$) C, H, N, S, Cl.

Optical Resolution of 12a. Method L. (i) L-Lysine monohydrochloride (3.85 g, 21 mmol) and a solution of KOH (1.18 g, 21 mmol) in MeOH (21 mL) were added successively to a solution of the nitro acid 12a (8.04 g, 20.95 mmol) in MeOH (110 mL) under ice cooling. The precipitated yellow needles were collected and

(16) Similarly, when methyl D-(4-hydroxyphenyl)glycinate was used, (−)-10a·methyl D-(4-hydroxyphenyl)glycinate salt (mp 168–171 °C (from EtOH); $[\alpha]^{20}_D$ −316.5° (*c* = 1.34, DMF)) was obtained. Anal. ($C_{16}H_{18}ClNO_4S$·$C_9H_{11}NO_3$) C, H, N, Cl.

(17) Bourdais, J. France Patent 1443917/65; *Chem. Abstr.* **1967**, *66*, 37933v. Battistini, P.; Bruni, P.; Fava, G. *Gazatta Chimica Italiana* **1980**, *110*, 301.

Table X. Effect of the *N,N*-Dimethylamino Derivatives on Vertebral and Coronary Blood Flows



compd	X	R	increase in vertebral blood flow in anesthetized dogs (ia, $N = 2$–5) potency ratio[a]	half duration,[b] min	increase in coronary blood flow in isolated guinea pig heart[c]
2a	6-Cl	Ac	0.62	53	++
2b	8-Cl		1.15	69	+++
(+)-2b	8-Cl		1.7	69	+++
(−)-2b	8-Cl		0.06	36	−
2w	8-Cl		0.01	31	−
2cc	9-Cl		0.75	72	+++
(+)-2cc	9-Cl		0.83	74	++++
(−)-2cc	9-Cl		0.06	22	−
2dd	8-F		0.37	71	++
2ii	9-F		0.34	43	++
2jj	7,8-Cl_2		0.51	53	+++
2kk	8,9-Cl_2		0.35	156	++
(+)-2ll	7-Cl		0.93	29	++
(−)-2ll	7-Cl		0.03	12	−
16a	6-Cl	H	0.20	33	+
16b	8-Cl		0.76	39	++
(+)-16b	8-Cl		0.94	46	++
(−)-16b	8-Cl		0.02	23	−
16m	9-Cl		0.91	52	+++
(+)-16m	9-Cl		1.25	46	+++
(−)-16m	9-Cl		0.02	21	−
16n	8-F		0.37	40	++
16o	9-F		0.14	33	++
16p	7,8-Cl_2		0.29	36	++
16q	8,9-Cl_2		0.62	80	+++
(+)-16r	7-Cl		0.17	24	−
diltiazem	H	Ac	1.00	53	+++

[a] Diltiazem = 1. [b] Duration of a half of the maximum change in blood flow. [c] The increase in CBF by more than 0.5 mL/min at the dose of 100, 30, 10, and 3 μg/heart is expressed as +, ++, +++, and ++++, respectively; − denotes the increase less than 0.5 mL/min at a dose of 100 μg/heart.

recrystallized from DMF–H_2O (1:1) twice to give 4.29 g (38.5%) of (+)-12a L-lysine salt: mp 244–246 °C. Anal. ($C_{22}H_{25}ClN_2O_6S$) C, H, N, S, Cl.

The mother liquors were combined, concentrated, and allowed to stand at room temperature. The precipitate was collected and recrystallized from DMF–H_2O (1:1) to give 3.61 g (32.4%) of (−)-12a L-lysine salt, mp 229–232 °C. Anal. ($C_{22}H_{28}ClN_2O_6S$) C, H, N, S, Cl.

(ii) (+)-12a L-lysine salt (4.29 g, 8.09 mmol) was suspended in water (100 mL), acidified with dilute HCl, and extracted with $CHCl_3$. The extracts were combined, washed with water, dried, and concentrated. The residue was recrystallized from *i*-PrOH to give 3.51 g (97.8%) of (+)-12a: mp 93–97 °C; $[\alpha]^{20}_D$ +158.7° (c = 0.708, $CHCl_3$); IR (Nujol) 3400, 1660 cm^{-1}; ^1H NMR (DMSO-d_6, 90 MHz) δ 3.72 (s, 3 H, OCH_3), 4.35 (d, J = 5.3 Hz, 1 H), 4.98 (d, J = 5.3 Hz, 1 H), 6.87 (d, J = 8.8 Hz, 2 H), 7.3–7.7 (m, 4 H), 8.07 (d, J = 8.8 Hz, 1 H). Anal. ($C_{18}H_{14}ClNO_6S$-*i*-PrOH) C, H, N, S, Cl.

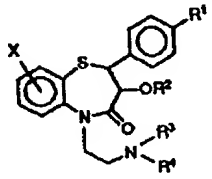
Similarly, (−)-12a (mp 92–97 °C; $[\alpha]^{20}_D$ −155.6° (c = 0.672, $CHCl_3$)) was obtained in 92.6% yield from (−)-12a L-lysine salt. Anal. ($C_{16}H_{14}ClNO_6S$-*i*-PrOH) C, H, N, S, Cl; N: Calcd, 3.16; found, 3.68.

(+)-*cis*-8-Chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4-(5*H*)-one ((+)-16b). Method M. A mixture of (+)-5b (20 g, 59.56 mmol), 2-(dimethylamino)ethyl chloride hydrochloride (9.4 g, 65.26 mmol), K_2CO_3 (24.7 g, 178.8 mmol), acetone (500 mL), and H_2O (5 mL) was stirred vigorously under reflux for 17 h. After cooling, inorganic compounds were filtered off and the filtrate was concentrated. The residual oil was triturated with *i*-Pr_2O and recrystallized from AcOEt–*n*-hexane to give 22.37 g (92.3%) of (+)-16b: mp 122–124 °C; $[\alpha]^{20}_D$ +141.8° (c = 1.00, MeOH); IR (Nujol) 3400–2800 (broad), 1675, 1610 cm^{-1}; EIMS m/z 406; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.25 (s, 6 H, NCH_3), 3.83 (s, 3 H, OCH_3), 2.3–3.0 (m, 2 H), 3.4–4.7 (m, 3 H), 4.88 (d, J = 7 Hz, 1 H), 6.88 (d, J = 8.7 Hz, 2 H), 7.3–7.8 (m, 5 H). Anal. ($C_{20}H_{23}ClN_2O_3S$) C, H, N, Cl. Oxalate: mp 201–203 °C (from EtOH–$CHCl_3$–Et_2O); $[\alpha]^{20}_D$ +78.4° (c = 0.74, DMF). Anal. ($C_{22}H_{25}ClN_2O_7S$) C, H, N, S, Cl; C: Calcd, 53.17; found, 52.72.

Method N. A mixture of (+)-5b (1.50 g, 4.47 mmol) and 96% KOH (574 mg, 4.82 mmol) in DMSO (25 mL) was stirred under ice cooling for 1 h. 2-(Dimethylamino)ethyl chloride hydrochloride (708 mg, 4.91 mmol) was added to the reaction mixture under ice cooling. The mixture was stirred at room temperature for 22 h, poured onto cracked ice, and extracted with EtOAc. The extracts were combined and extracted with 10% HCl. The aqueous layer was made basic with K_2CO_3 and extracted with AcOEt. The extracts were combined, washed with water, dried, and concentrated. The residual solid was recrystallized from EtOAc–*n*-hexane to give 1.33 g (73.1%) of (+)-16b.

(+)-*cis*-5-[2-(*N*-Allyl-*N*-methylamino)ethyl]-8-chloro-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one ((+)-16i). Method P. A mixture of (+)-17[10] (770 mg, 1.96 mol), allyl bromide (249 mg, 2.06 mmol), K_2CO_3 (1.0 g, 7.26 mmol), and DMF (10 mL) was stirred at room temperature overnight. AcOEt (100 mL) and H_2O (30 mL) were added to the reaction mixture, and AcOEt layer was separated, washed with water, dried, and concentrated. The residual oil was converted into the fumarate and recrystallized from EtOH–Et_2O to give 822 mg (77%) of (+)-16i: mp 136.5–138.5 °C; $[\alpha]^{20}_D$ +97.7° (c = 1.00, MeOH); IR (Nujol) 3440, 1680, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 2.15 (s, 3 H, NCH_3), 3.76 (s, 3 H, OCH_3), 4.21 (d, J = 7 Hz, 1 H, 3-H), 4.90 (d, J = 7 Hz, 2-H), 2.96 (d, J = 6.5 Hz, 2 H, CH_2—CH=CH_2), 4.95–5.20 (m, 2 H, =CH_2), 5.4–5.8 (m,

Table XI. Effect of New 1,5-Benzothiazepine Derivatives on Vertebral and Coronary Blood Flows



compd	X	R^1	R^2	R^3	R^4	increase in vertebral blood flow in anesthetized dogs (1a, N = 2–5) potency ratio[a]	half duration,[b] min	increase in coronary blood flow in isolated guinea pig heart[c]
(+)-2b	Cl	OMe	Ac	Me	Me	1.7	69	+++
(+)-2c	Cl	OMe	CHO	Me	Me	0.73	44	++
(+)-2d	Cl	OMe	COEt	Me	Me	1.45	64	+++
(+)-2e	Cl	OMe	CO*n*-Pr	Me	Me	0.80	41	++++
(+)-2f	Cl	OMe	CO*n*-Bu	Me	Me	0.67	42	++++
2g	Cl	OMe	CONH*n*-Bu	Me	Me	0.31	76	+++
2h	Cl	OMe	CO_2Et	Me	Me	0.29	44	+
2i	Cl	OMe	4-NO_2Bz[d]	Me	Me	0.05	75	++
(+)-2j	Cl	OMe	4-NO_2-2-ClBz	Me	Me	0.08	118	++
2l	Cl	OMe	4-MeBz	Me	Me	0.33	140	NT[e]
(+)-2m	Cl	OMe	Me	Me	Me	0.58	47	+++
(+)-2n	Cl	OMe	4-NO_2Bzl[d]	Me	Me	0.58		NT
2o	Cl	OMe	Ac	Me	Et	0.74	60	++
(+)-2o	Cl	OMe	Ac	Me	Et	0.90	46	++
2q	Cl	OMe	Ac	Me	*n*-Pr	0.50	47	+++
(+)-2r	Cl	OMe	Ac	Me	$CH_2CH{=}CH_2$	1.00	37	NT
(+)-2u	Cl	OMe	Ac	Et	Et	0.55	48	+
(+)-16b	Cl	OMe	H	Me	Me	0.94	46	++
16d	Cl	OMe	H	Me	Et	0.28	38	++
16e	Cl	OMe	H	Me	*n*-Pr	0.24	35	++
(+)-16f	Cl	OMe	H	Et	Et	0.32	31	-
(+)-16i	Cl	OMe	H	Me	$CH_2CH{=}CH_2$	0.23	34	NT
(+)-16j	Cl	OMe	H	Me	$CH_2C{\equiv}CH$	0.06	28	NT
2x	Cl	Me	Ac	Me	Me	0.37	61	NT
2y	Cl	Me	4-NO_2Bz	Me	Me	0.08	84	NT
2z	Cl	Me	4-NO_2-2-ClBz	Me	Me	0.05	156	NT
2aa	Cl	Me	4-Cl-2-NO_2Bz	Me	Me	0.02	140	NT
16l	Cl	Me	H	Me	Me	0.52	31	NT
(+)-2p	Cl	OMe	Me	Me	Et	0.50	41	++++
16k	Cl	SMe	H	Me	Me	0.09	35	+
2bb	Cl	SMe	Ac	Me	Me	0.21	37	+
2dd	F	OMe	Ac	Me	Me	0.37	71	++
2ee	F	OMe	CONH*n*-Bu	Me	Me	0.16	58	+++
2ff	F	OMe	CO_2Et	Me	Me	0.16	33	++
2gg	F	OMe	4-NO_2Bz	Me	Me	0.35	48	+++
2hh	F	OMe	4-MeBz	Me	Me	0.26	62	++++

[a] See footnote *a* in Table X. [b] See footnote *b* in Table X. [c] See footnote *c* in Table X. [d] Bz = benzoyl; Bzl = benzyl. [e] Not tested.

1 H, —CH=), 6.86 (d, J = 8.8 Hz, 2 H), 7.33 (d, J = 8.8 Hz, 2 H), 7.3–7.8 (m, 3 H). Anal. ($C_{22}H_{25}ClNO_3S$-$C_4H_4O_4$) C, H, N, S, Cl.

(+)-*cis*-3-Acetoxy-8-chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4-(5*H*)-one ((+)-2b). Method Q. A mixture of (+)-16b (54.47 g, 134 mmol), Ac_2O (545 mL), and pyridine (5.5 mL) was heated at 100 °C for 4 h and concentrated. The residual oil was converted into the maleate and recrystallized from EtOH to give 122.9 g (90.9%) of (+)-2b maleate: mp 160.5–161.5 °C; $[\alpha]^{20}_D$ +76.5° (c = 1.00, MeOH); IR (Nujol) 2700–2100, 1765, 1685, 1610 cm^{-1}; EIMS m/z 448, 447, 212, 170; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.90 (s, 3 H, $COCH_3$), 2.90 (s, 6 H, NCH_3), 3.4 (m, 2 H), 3.82 (s, 3 H, OCH_3), 4.3 (m, 2 H), 5.03 (d, J = 7.8 Hz, 1 H), 5.09 (d, J = 7.8 Hz, 1 H), 6.25 (s, 2 H, maleic acid), 6.90 (d, J = 8.8 Hz, 2 H), 7.35 (d, J = 8.8 Hz, 2 H), 7.37 (d, J = 8.7 Hz, 1 H), 7.54 (dd, J = 8.7 and 2.2 Hz, 1 H), 7.72 (d, J = 2.2 Hz, 1 H). Anal. ($C_{22}H_{25}ClN_2O_4S$-$C_4H_4O_4$) C, H, N, Cl, S.

(+)-*cis*-8-Chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-3-(valeryloxy)-1,5-benzothiazepin-4-(5*H*)-one ((+)-2f). Method R. To a solution of (+)-16b (900 mg, 2.21 mmol) in pyridine (1 mL) was added valeryl chloride (300 mg, 2.49 mmol) under ice cooling. The mixture was stirred at room temperature for 3 h and concentrated. The residual oil was worked up in the usual manner and converted into the oxalate to give 1.22 g (94.8%) of (+)-2f oxalate: mp 167–169 °C (from EtOH); $[\alpha]^{20}_D$ +56.4° (c = 0.328, MeOH); IR (Nujol) 2800–2200, 1730, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.79 (t, J = 6 Hz, 3 H, CH_3), 1.0–1.8 (m, 4 H, CH_2), 2.15 (t, J = 6 Hz, CH_2CO), 2.91 (s, 6 H, NCH_3), 3.81 (s, 3 H, OCH_3), 5.05 (s, 2 H, 2- and 3-H), 6.90 (d, J = 8.7 Hz, 2 H), 7.2–7.8 (m, 5 H). Anal. ($C_{25}H_{31}ClN_2O_4$-S-$C_2H_2O_4$) C, H, N, S, Cl.

***cis*-3-[[(*n*-Butylamino)carbonyl]oxy]-8-chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one ((±)-2g). Method S.** A mixture of (±)-16b (920 mg, 2.26 mmol), *n*-butyl isocyanate (674 mg, 6.80 mmol), Et_3N (1 drop), and benzene (15 mL) was heated under reflux for 44 h and concentrated. The residue was converted into the hydrochloride and recrystallized from $CHCl_3$–EtOH–Et_2O to give 1.05 g (85.6%) of (±)-2g·HCl: mp 142–144 °C dec; IR (Nujol) 3400, 3280, 2800–2000, 1715, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.86 (bt, 3 H, CH_3), 1.0–1.5 (m, 4 H, CH_2), 2.89 (s, 6 H, NCH_3), 3.82 (s, 3 H, OCH_3), 5.07 (s, 2 H, 2- and 3-H), 6.91 (d, J = 8 Hz, 2 H), 7.3–7.5 (m, 5 H). Anal. ($C_{25}H_{32}ClN_3O_4S$·HCl) C, H, N, Cl.

(+)-*cis*-8-Chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-3-methoxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4-

Table XII. Hypotensive Activity in SHR

compd	change in blood pressure (Δ mmHg) at the dose of 30 mg/kg (N = 3–6): a period of time after dosing	
	1 h	4 h
16a	−31.7	−26.0
(+)-16b	−13.3	−51.7
(−)-16b	+1.0	−20
16d	−21.3	−39.3
16e	−20.0	−27.3
(+)-16m	−46.7	−30.0
2a	−22.0	−13.7
(+)-2b	−86.0	−68.0
(−)-2b	−6.0	−22.7
(+)-2c	−60.0	−72.7[a]
(+)-2d	−67.7	−60.7[a]
(+)-2e	−30.0	−28.0
(+)-2f	−46.0	−39.0
(+)-2m	−76.8	−56.5[b]
(+)-2n	−11.5	−8.8[b]
(+)-2o	−55.5	−22.3[b]
2q	−16.0	−9.0
(+)-2r	−29.0	−17.0[b]
(+)-2cc	−73.7	−54.3
2dd	−64.0	−50.0
2ii	−39.0	−60.3
diltiazem	−34.0	−15.0

[a] At the dose of 100 mg/kg. [b] 5 h after dosing.

(5*H*)-one ((+)-2m). Method T. NaH (60%, dispersion in mineral oil, 590 mg, 14.75 mmol) was added to a solution of (+)-16b (4.0 g, 9.83 mmol) in toluene (50 mL) and DMSO (2 mL) under ice cooling. After the mixture was stirred at 30–40 °C for 30 min, Me_2SO_4 (1.36 g, 10.86 mmol) was added to the mixture under ice cooling and the mixture was stirred at 50–60 °C for 4.5 h, diluted with water, and extracted with AcOEt. The extracts were combined, washed with water, dried, and concentrated. The residual oil was converted into the hydrochloride and recrystallized from MeOH–Et_2O to give 2.77 g (61.5%) of (+)-2m hydrochloride: mp 245–248 °C; $[\alpha]^{20}_D$ +60.7° (c = 0.287, MeOH); IR (Nujol) 2700–2200, 1680 cm^{-1}; ^{1}H NMR (DMSO-d_6, 90 MHz) δ 2.79 (s, 6 H, NCH_3), 3.08 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 4.03 (d, J = 7 Hz, 1 H, 3-H), 5.14 (d, J = 7 Hz, 1 H, 2-H), 6.85 (d, J = 8 Hz, 2 H), 7.33 (d, J = 8 Hz, 2 H), 7.5–7.9 (m, 3 H). Anal. ($C_{21}H_{25}ClN_2O_3S$·HCl) C, H, N, S, Cl.

(+)-*cis*-8-Chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-3-[(4-nitrobenzyl)oxy]-1,5-benzothiazepin-4(5*H*)-one ((+)-2n). Method U. A mixture of (+)-16b (3.6 g, 8.85 mmol) and 63% NaH (337 mg, 8.85 mmol) in toluene (30 mL) was warmed at 40 °C for 30 min. Then, a solution of 4-nitrobenzyl bromide (1.92 g, 8.85 mmol) in toluene (30 mL) was added to the reaction mixture at room temperature. After 2 h of stirring, concentrated NH_4OH (30 mL) was added to the reaction mixture and the mixture was stirred at room temperature for 1 h, diluted with AcOEt, washed with 10% HCl, water, 10% K_2CO_3, and water, successively, dried, and concentrated. The residual oil was separated by column chromatography (silica gel, eluted with 2.5% MeOH–$CHCl_3$). Conversion of the first eluate into the oxalate and recrystallization from *i*-PrOH–EtOH gave 1.05 g (17%) of (+)-2n oxalate: mp 99.5–109 °C; $[\alpha]^{20}_D$ −16.9° (c = 0.630, MeOH); IR (Nujol) 3480, 2700–2150, 1725, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$, free base) δ 2.26 (s, 6 H, NCH_3), 3.81 (s, 3 H, OCH_3), 4.17 (d, J = 7 Hz, 1 H, 3-H), 4.28 (d, J = 12 Hz, 1 H, CH_2Ar), 4.62 (d, J = 12 Hz, 1 H, CH_2Ar), 5.02 (d, J = 7 Hz, 1 H, 2-H), 6.62–8.11 (m, 11 H). Anal. ($C_{27}H_{28}ClN_3O_5S$·$C_2H_2O_4$·$^1/_3$EtOH·$^1/_3$-*i*-PrOH) C, H, N, S, Cl.

Pharmacology. Effect on Vertebral Blood Flow in Anesthetized Dogs. Male or female mongrel dogs were anesthetized with sodium pentobarbital (PB, 30–35 mg/kg, iv) and artificially ventilated. Throughout the experiment, PB (3–5 mg/kg per h) was continuously infused into femoral vein to keep anesthesia constant. Right vertebral artery was exposed, and the blood flow was measured by a electromagnetic flowmeter (MFV-2100 or MF-27; Nihon-Kohden, Tokyo, Japan). Test compounds and diltiazem dissolved in saline were directly administered into the right vertebral artery via a cannula inserted into the vertebral artery.

From the values of peak response, we obtained the dose–response curve. Increasing effect of the tested compounds on vertebral blood flow were expressed as the potency ratio to that of diltiazem calculated from the dose–response curves.

Effect on Coronary Blood Flow in Isolated Guinea Pig Hearts. Isolated hearts from Hartley guinea pigs were perfused according to Langendorff's method with modified Locke–Ringer solution containing defibrinated rabbit blood (perfusion pressure; 40 cm H_2O, temperature of perfusate; 29 ± 1 °C). Out flow of perfusate, i.e. coronary blood flow, was measured by means of a drop counter method. Test compounds were dissolved in saline and administered into aortic cannula. If coronary blood flow increased by 0.5 mL/min or more at doses of 3, 10, 30, and 100 μg/heart, we judged the response was "++++", "+++", "++" and "+", respectively. If coronary blood flow increased less than 0.5 mL/min at 100 μg/heart, we judged the response was "−".

Hypotensive Action in SHR. Male spontaneously hypertensive rats (SHR) which had been fasted for 20 h previously were used. Blood pressure was measured by means of a tail-cuff method in conscious state. Test compounds dissolved in deionized water were administered orally. Hypotensive action was expressed in terms of changing value of blood pressure from predosing value at 1 and 4 h, and/or 1 and 5 h after the dosing.

X-ray Crystallographic Analysis. The diffraction experiment was carried out with use of a colorless transparent prism with dimension of 0.5 × 0.2 × 0.2 mm^3. The four-circle diffractometer (AFC/5, RIGAKU) was used with graphite-monochromated Cu Kα radiation (λ = 1.5418 Å). The unit cell dimensions were determined from angular setting of 25 reflections (2θ values in the range of 30–60°). The crystal data are as follows: $C_{22}H_{25}N_2O_4SCl$·$C_4H_4O_4$; MW = 565.04; a = 10.883 (1), b = 23.798 (2), c = 10.557 (1) Å; U = 2734.2 (4) Å^3; orthorhombic; space group $P2_12_12_1$; Z = 4; D_x = 1.372 g/cm; F(000) = 1184; μ(Cu Kα) = 7.323 cm^{-1}.

Three dimensional intensity data were measured by ω–2θ scan technique (2θ ≤ 130°). Unique reflections (2653) were measured, of which 2465 with $|F_o| \geq 2.67\sigma(F)$ were considered as observed. No absorption corrections were applied.

Analysis. The structure was solved by the direct methods with use of MULTAN 80.[18] The refinement of atomic parameters were carried out with use of block-diagonal matrix least-squares methods with anisotropic temperature factors for the non-hydrogen atoms. All hydrogen atoms were located on the difference Fourier maps and refined with isotropic temperature factors.

Throughout the refinement, the function $\sum w(|F_o| - |F_c|)^2$ was minimized.

During the final refinement stage, the weighting scheme of $\sqrt{W} = 1/\sigma(F_o)$ was used. The final R value was 0.045 (R_w = 0.055). $\Delta\rho$max = 0.2 e/Å^3.

The atomic scattering factors were taken from *International Tables for X-ray Crystallography*.[19]

Absolute Configuration. The absolute configuration was determined by Bijvoet pairs method.[20] The structure factors were calculated including anomalous scattering factors of all atoms for Cu Kα radiation.[19] The intensity data of the Bijvoet pairs, (h, k, l) and (h, $-k$, l), were measured precisely, in a right-handed set of coordinate axes.

Figure 1 shows the stereoscopic view of the molecule drawn in the right-handed set of coordinate axes, which shows the correct absolute configuration of the molecule as $C_2(S)$ and $C_3(S)$.

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(18) Main, *computer program* G.; Woolfson, M. M. *MULTAN 80: A computer program for automatic analysis of phase problem*; Univ. of York: England.
(19) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, 1974; Vol. IV.
(20) Bijvoet, J. M.; Peerdeman, A. F.; van Bommel, A. J. *Nature* 1951, *168*, 271.

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Registry No. (±)-2a, 130605-15-1; (±)-2a·HCl, 130884-46-7; (+)-2b, 96125-53-0; (+)-2b·HCl, 96125-52-9; (+)-2b·maleate, 96128-92-6; (−)-2b, 110284-22-5; (−)-2b·HCl, 96125-59-6; (−)-2b·maleate, 130979-49-6; (±)-2b, 96451-06-8; (±)-2b·HCl, 96125-24-5; (+)-2c, 96125-41-6; (+)-2b·oxalate, 96125-42-7; (+)-2d, 96125-43-8; (+)-2d·oxalate, 96125-44-9; (+)-2e, 96125-45-0; (+)-2e·oxalate, 96125-46-1; (+)-2f, 96125-47-2; (+)-2f·oxalate, 96125-48-3; (±)-2g, 130884-75-2; (±)-2g·HCl, 130884-47-8; (±)-2h, 130884-48-9; (±)-2h·HCl, 121628-83-9; (±)-2i, 122666-34-6; (+)-2i, 122666-30-2; (+)-2i·oxalate, 122666-72-2; (+)-2k, 122682-52-4; (+)-2k·fumarate, 122682-53-5; (±)-2l, 120701-21-5; (±)-2l·oxalate, 120701-22-6; (+)-2m, 131099-95-1; (+)-2m·HCl, 104975-70-4; (+)-2h, 130884-49-0; (+)-2h·oxalate, 130979-50-9; (+)-2o, 96125-36-9; (+)-2o·L-tartrate, 96125-37-0; (±)-2o, 96142-59-5; (±)-2o·HCl, 96125-29-0; (+)-2p, 130884-76-3; (+)-2p·fumarate, 130981-21-4; (±)-2q, 96125-28-9; (±)-2q·oxalate, 96125-31-4; (+)-2r, 130884-50-3; (+)-2r·oxalate, 130979-51-0; (+)-2s, 130884-51-4; (+)-2s·oxalate, 130884-52-5; (+)-2t, 100893-29-6; (−)-2t, 100893-21-8; (−)-2t·oxalate, 131099-96-2; (±)-2t, 100893-31-0; (±)-2t·HCl, 100893-32-1; (+)-2u, 96125-27-8; (+)-2u·oxalate, 96125-40-5; (+)-2v, 130884-53-6; (+)-2v·fumarate, 130884-54-7; (−)-2v, 100893-02-5; (−)-2v·fumarate, 131099-97-3; (±)-2w, 130979-52-1; (±)-2w·HCl, 130979-53-2; (±)-2w·oxalate, 130979-54-3; (±)-2x, 130884-55-8; (±)-2x·HCl, 130884-56-9; (±)-2x, 130884-57-0; (±)-2x·HCl, 122666-47-1; (±)-2z, 130884-58-1; (±)-2z·HCl, 122666-59-5; (±)-2aa, 130884-59-2; (±)-2aa·HCl, 122666-64-2; (±)-2bb, 130884-60-5; (±)-2bb·HCl, 130884-61-6; (+)-2cc, 103921-09-1; (+)-2cc·HCl, 103920-99-6; (−)-2cc, 103921-10-4; (−)-2cc·HCl, 103921-02-4; (±)-2cc, 130695-87-3; (±)-2cc·HCl, 103920-96-3; (±)-2dd, 100601-02-3; (±)-2dd·HCl, 100601-01-2; (±)-2ee, 130884-77-4; (±)-2ee·HCl, 130903-47-8; (±)-2ff, 130884-78-5; (±)-2ff·HCl, 121664-35-5; (±)-2gg, 122666-41-5; (±)-2gg·$^1/_2$oxalate, 122666-42-6; (±)-2hh, 120701-27-1; (±)-2hh·$^1/_2$oxalate, 120701-28-2; (±)-2ii, 100601-03-4; (±)-2ii·HCl, 100601-04-5; (±)-2jj, 100600-75-7; (±)-2jj·HCl, 100600-76-8; (±)-2kk, 100600-77-9; (±)-2kk·HCl, 100600-78-0; (+)-2ll, 130790-20-4; (+)-2ll·HCl, 130979-55-4; (−)-2ll, 130790-24-8; (−)-2ll·HCl, 130979-56-5; 3a, 40925-72-2; 3b, 1004-00-8; 3c, 23474-98-8; 3d, 14482-33-8; 3e, 33264-82-3; 3f, 100493-32-1; 3 (X = 5,6-Cl$_2$), 6647-25-2; 3 (X = 4,6-Cl$_2$), 6647-24-1; (±)-4a, 96125-49-4; (±)-4b, 100493-13-8; (±)-4c, 130884-62-7; (±)-5a, 130884-63-8; (+)-5b, 96142-63-1; (−)-5b, 96125-56-3; (±)-5b, 96125-60-9; (±)-5c, 130884-64-9; (±)-5d, 122666-79-9; (±)-5e, 100902-58-7; (2*S*,3*S*)-5e, 100902-62-3; (2*R*,3*R*)-5e, 100902-60-1; (±)-5f, 100492-87-3; (±)-5g, 100492-85-1; (±)-5h, 100493-29-6; (±)-5i, 100601-38-5; (±)-5j, 100601-39-6; (+)-5k, 130979-57-6; (−)-5k, 130979-58-7; (±)-6a, 130884-65-0; (±)-6b, 96125-50-7; (±)-6h, 100601-58-9; (±)-6j, 100601-57-8; (±)-7a, 96142-62-0; (±)-7b, 122666-77-7; (±)-7c, 103921-06-8; (±)-7d, 100493-33-2; (±)-7e, 130884-66-1; (±)-8a, 96087-08-0; (±)-8b, 103921-05-7; (±)-9a, 130979-64-5; (+)-10a, 96054-27-2; (+)-10a·methyl L-(4-hydroxyphenyl)glycinate, 96054-28-3; (−)-10a, 96054-29-4; (−)-10a·methyl D-(4-hydroxyphenyl)glycinate, 96054-30-7; (±)-10a, 96125-51-8; (±)-10b, 122666-78-8; (−)-10c, 100902-61-2; (±)-10c, 103921-07-9; (±)-11a, 130884-67-2; (+)-12a, 96125-22-3; (+)-12a·L-lysine, 104966-84-9; (−)-12a, 96125-23-4; (−)-12a·L-lysine, 130884-68-3; (±)-12a, 96125-21-2; (±)-13a, 130979-65-6; 14a, 611-07-4; 14b, 603-86-1; (2*R*,3*R*)-15a, 100938-15-6; (2*S*,3*S*)-15a, 100902-59-8; (±)-16a, 130605-16-2; (±)-16a·HCl, 130884-69-4; (+)-16b, 96125-25-6; (+)-16b·oxalate, 96125-26-7; (−)-16b, 96125-57-4; (−)-16b·oxalate, 96125-58-5; (±)-16b, 105487-93-2; (±)-16b·HCl, 96125-61-0; (±)-16c, 130979-60-1; (+)-16d, 96125-34-7; (+)-16d·HClO$_4$, 96125-35-8; (±)-16d, 105487-94-3; (±)-16d·HCl, 96125-62-1; (±)-16e, 96087-06-8; (±)-16e·HBr, 96125-30-3; (+)-16f, 96125-38-1; (+)-16f·fumarate, 96125-39-2; (+)-16g, 131062-93-6; (+)-16g·HCl, 130979-61-2; (−)-16g, 100892-88-4; (−)-16g·HCl, 100892-89-5; (+)-16h, 100893-27-4; (+)-16h·HClO$_4$, 100893-28-5; (−)-16h, 100893-18-3; (−)-16h·HClO$_4$, 131099-98-4; (±)-16h, 100893-24-1; (±)-16h·oxalate, 130884-70-7; (+)-16i, 130884-71-8; (+)-16i·fumarate, 130979-62-3; (+)-16g, 130979-63-4; (+)-16j·HCl, 130884-72-9; (±)-16k, 130884-73-0; (±)-16k·HCl, 130884-74-1; (±)-16l, 122666-80-2; (+)-16m, 103920-97-4; (+)-16m·HClO$_4$, 103920-98-5; (−)-16m, 103921-00-2; (−)-16m·HClO$_4$, 103921-01-3; (±)-16m, 103920-95-2; (±)-16m·HCl, 103921-04-6; (±)-16n, 100601-05-6; (±)-16n·HCl, 100601-06-7; (±)-16o, 100601-07-8; (±)-16o·HCl, 100601-08-9; (±)-16p, 100600-97-3; (±)-16p·HCl, 100600-98-4; (±)-16q, 100600-99-5; (±)-16q·HCl, 100601-00-1; (+)-16r, 130790-21-5; (−)-16r, 130790-25-9; (+)-17, 110284-39-4; (*S*)-*N*-(2-naphthylsulfonyl)-2-pyrrolidinecarbonyl chloride, 91872-31-0.

Supplementary Material Available: Tables of structural data including Table XIII, giving final atomic coordinates and equivalent isotropic or isotopic thermal parameters with esd in parentheses, Table XIV, giving bond lengths with esd in parentheses, Table XV, giving bond angles with esd in parentheses, and Table XVI, giving results of Bijvoet pairs measurements and Figure 3, giving atomic nomenclature (5 pages); listing of structure factors (8 pages). Ordering information is given on any current masthead page.

Muscarinic Cholinergic Agonists and Antagonists of the 3-(3-Alkyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine Type. Synthesis and Structure–Activity Relationships

Per Sauerberg,* Jens W. Kindtler, Lone Nielsen, Malcolm J. Sheardown, and Tage Honoré

Ferrosan A/S, CNS Division, Sydmarken 5, DK-2860 Soeborg, Denmark. *Received April 4, 1990*

A series of 3-(3-alkyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydro-1-methylpyridines (2a–q) were synthesized and tested for central muscarinic cholinergic receptor binding affinity by using [^{3}H]oxotremorine-M and [^{3}H]QNB as ligands and in a functional assay using guinea pig ileum. The analogues with unbranched C_{1-5}-alkyl substituents (2a–g) were agonists, whereas the compounds with branched or cyclic substituents (2h–m) were antagonists. The alkyl ether analogues (2o–q) were also agonists but had lower receptor binding affinity than the corresponding alkyl analogues. The 3-(5-alkyl-1,2,4-oxadiazol-3-yl)-1,2,5,6-tetrahydro-1-methylpyridine analogues had only very low affinity for the central muscarinic receptors and were weak antagonists in the ileum assay. A few 3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydro-1-methylpyridines substituted with methyl or hydrogen in the 1-, 5-, or 6-position were synthesized and tested. *N*-Desmethyl analogue 7 was a potent muscarinic agonist, whereas *N*-desmethyl-5-methyl analogue 11 and *N*-methyl-6-methyl analogue 13 both were antagonists with lower muscarinic receptor affinity. The 3-(3-butyl-1,2,4-oxadiazol-5-yl)quinuclidine (17) and tropane (15) analogues were both very potent antagonists with high affinity for central muscarinic receptors. The ratio [IC_{50}(QNB)/IC_{50}(Oxo-*M*)] × 0.162 proved to be a good indicator of the efficacy of the compounds in the guinea pig ileum assay.

The finding of a cholinergic deficit in the brain of patients with Alzheimer's disease has lead to the cholinergic hypothesis of Alzheimer's disease and to attempts at restoring cholinergic function by means of cholinomimetic

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